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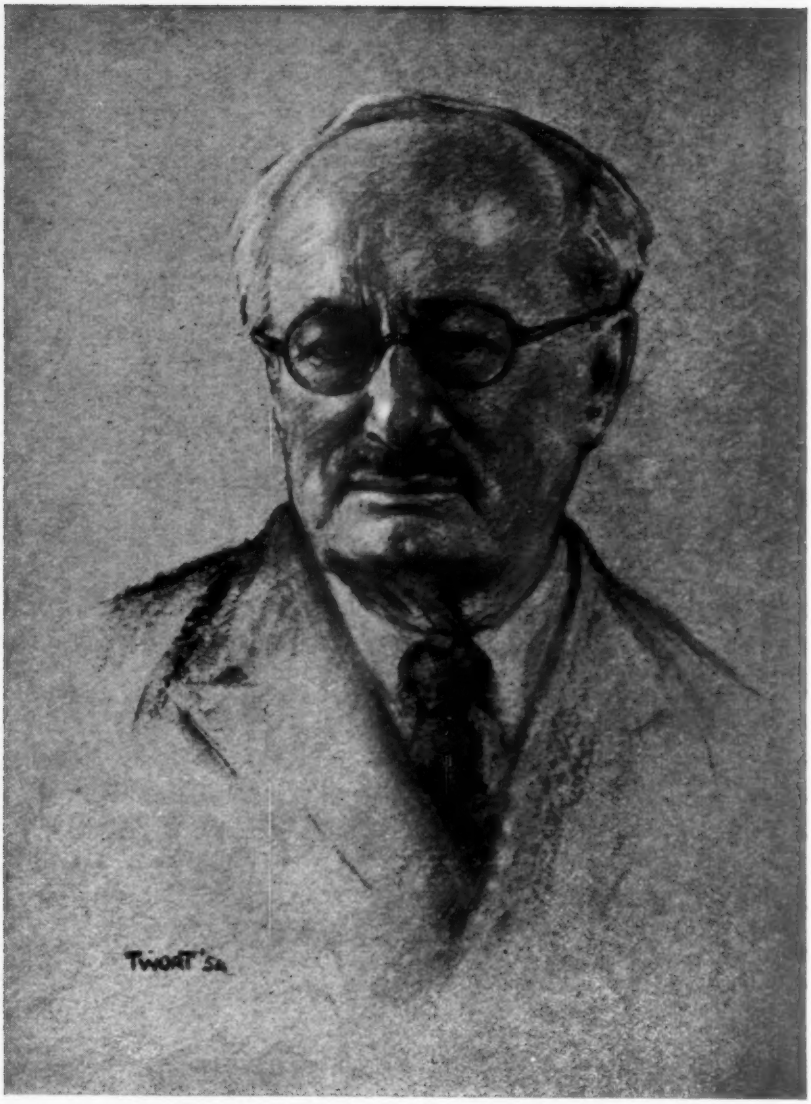

LORD HORDER

[*facing p. 225*

LORD HORDER

Lord Horder died on August 13, 1955, at the age of 84. He was the senior member of the Editorial Board of the *Annals*, and had been chairman of the Empire Rheumatism Council from its foundation in 1936 until his retirement in 1953. He had also been President of the Heberden Society. Although he was the greatest British clinician of his time and had lived through a period of revolutionary change in the science of medicine and in the organization of its services to the public, his amazing and undimmed mental and physical energy made him completely master of the rapidly changing scene. The incidence of rheumatism—at a time when this disease group was hardly a respectable field of study—was a major concern of his, and his period of chairmanship of the Empire Rheumatism Council did much to dispel the profound apathy which prevailed, both in the medical profession and among the lay public in Great Britain.

He will be much missed in the international field of rheumatology. Few men can have lived a life so long, so full of service right to its sudden end.

W.S.C.C.

Ann. rheum. Dis. (1955), **14**, 226.

DIPHENYLAMINE REACTION IN RHEUMATOID ARTHRITIS

BY

G. R. FEARNLEY, JEANETTE PIRKIS, NANETTE DE COEK, RITA LACKNER, AND R. I. MEANOCK

From the Department of Medicine, Postgraduate Medical School of London

(RECEIVED FOR PUBLICATION MAY 25, 1955)

From time to time new tests purporting to measure activity in rheumatic disease are described. Such a test is the colour intensity obtained when a protein-free precipitate of plasma or serum is treated with Dische's diphenylamine reagent under defined conditions (Ayala and others, 1951). The blood reactant is a mucoprotein or mucoprotein derivative, and the reaction has considerable theoretical interest. Coburn and others (1953), who found it to be a useful measure of activity in rheumatic fever, has reported interesting changes shown by this reaction in experimental arthritis (Coburn and Haninger, 1954).

For the practical purpose of measuring rheumatic activity in patients, however, any new test is acceptable only if it can be shown to be superior to the erythrocyte sedimentation rate which, for ease and simplicity, almost defies competition. We, therefore, decided to investigate the reaction in patients with rheumatoid arthritis and to compare it with the erythrocyte sedimentation rate (Westergren method). The objects of the investigation were as follows:

(1) How does the diphenylamine reaction correlate with the E.S.R.?
(2) What is the response in patients given steroid therapy?
(3) Is the test of any value as a measure of activity in the small number of patients with clinically active rheumatoid arthritis and normal sedimentation rates?

Material

Controls.—32 subjects aged between 20 and 60 years, who had no evidence of disease.

Patients.—23 subjects with rheumatoid arthritis, aged between 20 and 70 years.

Method

The semimicro procedure of Ayala and others (1951) was used on heparinized plasma. Readings were made with a Unicam spectrophotometer at 530 μ. Results are given in optical density × 1,000. Duplicates gave an error of not greater than 2 per cent.

Results

Fig. 1 (opposite) shows readings obtained from 37 estimations on 32 healthy subjects, range 210-310 (mean 250; S.D. 26·6), and from 34 estimations on 23 patients with clinically active rheumatoid arthritis, range 230-420.

Fig. 2 (opposite) shows diphenylamine readings plotted against erythrocyte sedimentation rates of patients and controls (correlation coefficients were 0·66 and 0·60). It is thus apparent that diphenylamine levels are raised in patients with active rheumatoid arthritis, and that there is a reasonable correlation between the diphenylamine readings and the sedimentation rates.

Serial Observations.—Fig. 3 shows the results obtained in a male patient aged 26 who went into remission when given aspirin in a dosage of 100 gr. daily. It will be seen that a considerable fluctuation occurred in the diphenylamine level, but not in the E.S.R.

Fig. 4 shows the response of a female patient aged 31 with clinically very active rheumatoid arthritis, whose E.S.R. was barely raised and whose diphenylamine level was within normal limits when Acthar gel was started. It will be seen that both fell during therapy, which was attended by great clinical improvement.

Fig. 5 shows the response obtained in a male

patient aged 21 with Reiter's syndrome who was treated with Acthar gel. In this patient the E.S.R. and the plasma diphenylamine level fell in parallel. Study of the chart suggests that this patient's arthritis was probably going into remission before therapy was started.

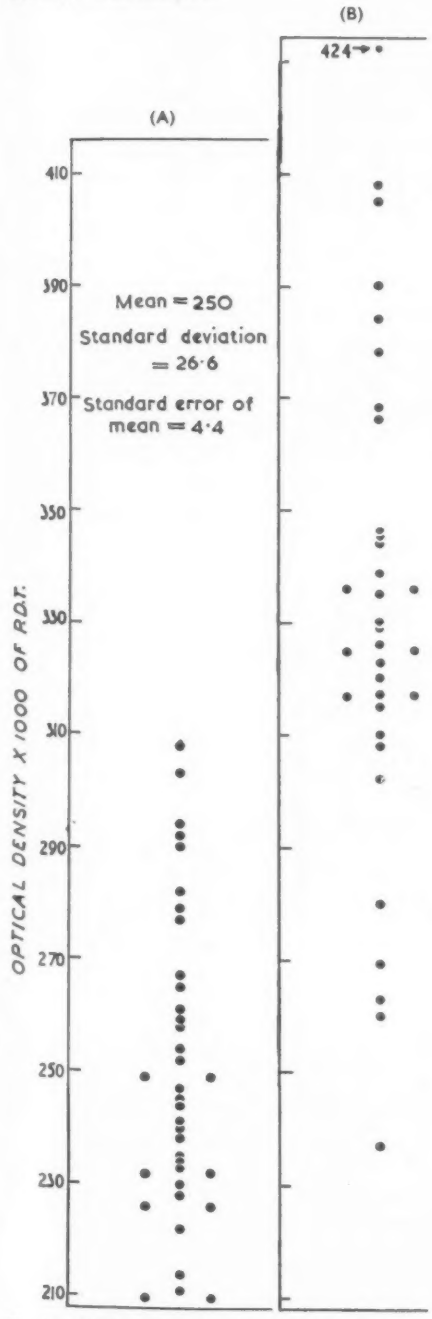

Fig. 1.—Diphenylamine levels in (A) 32 normal subjects (37 readings) and (B) 23 arthritic subjects (34 readings).

Fig. 6 (female aged 65) and Fig. 7 (male aged 38) show the changes encountered in two further patients with rheumatoid arthritis treated with Acthar gel. In both, and especially in the latter, there were unexplained fluctuations in the diphenylamine level which were not paralleled by the E.S.R.

Fig. 6 shows that the E.S.R. and the diphenylamine level both rebounded sharply when the dosage of Acthar gel was reduced. Replacement by "Butazolidin" then appeared to cause a reduction in both levels, but this drug was not continued long enough to determine whether the downward trend would have been maintained.

Relation between Diphenylamine Level, E.S.R., and Clinical Activity

In 34 determinations on patients with clinically active rheumatoid arthritis, 27 were found to have a raised erythrocyte sedimentation rate (over 15 mm./hr, Westergren) and 25 of these also had a raised diphenylamine level (over 304—optical density × 1,000); of the seven arthritics with a normal E.S.R., only two had a raised diphenylamine level.

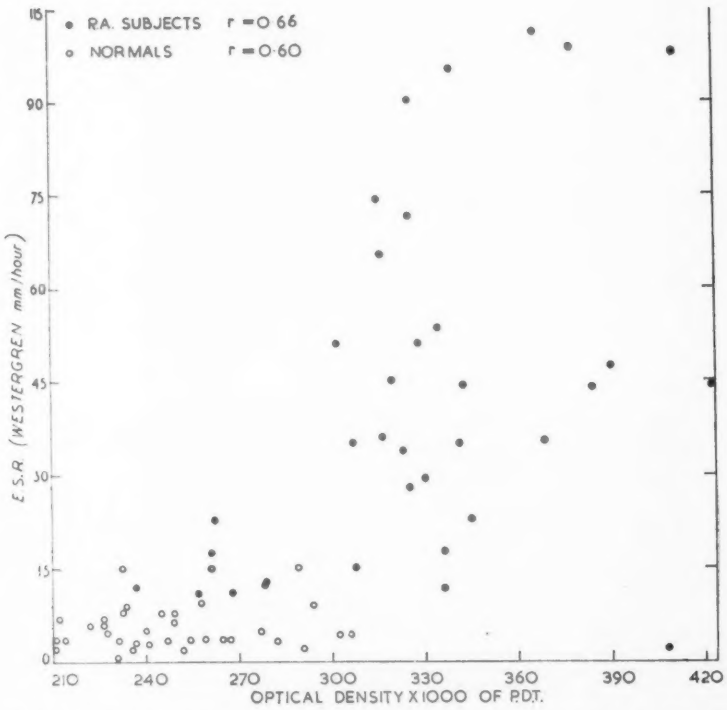

Fig. 2.—Correlation between erythrocyte sedimentation rate and P.D.T. in normal subjects and arthritics.

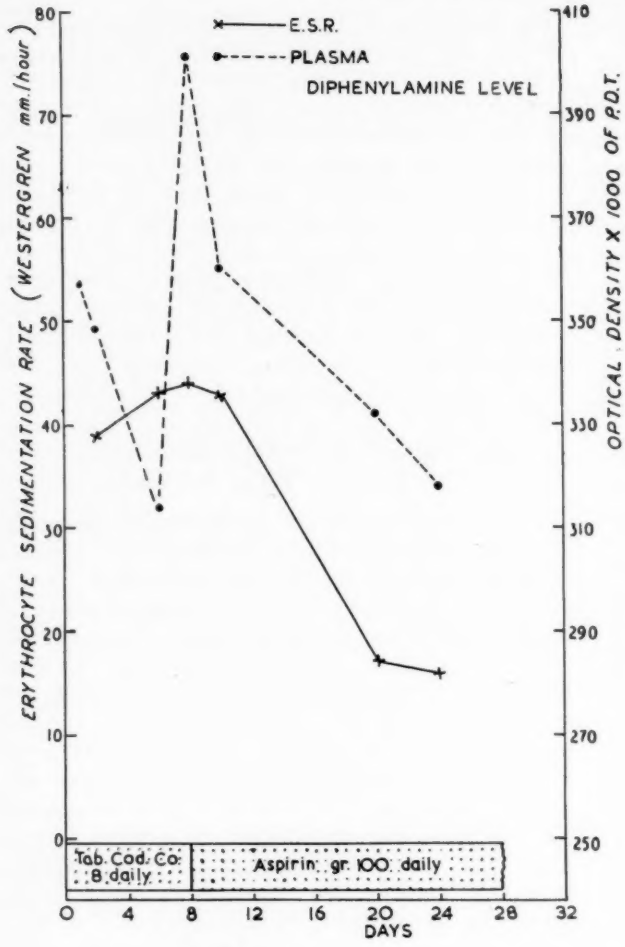

Fig. 3.—Results in a male patient aged 26.

Comment.—In something like 10 per cent. of patients with rheumatoid arthritis who show clinical evidence of activity, the erythrocyte sedimentation rate lies within the generally accepted range of normality. This is not taken to mean normality for a given individual, as it is obvious that a Westergren E.S.R. reading of 14 mm./hr would represent an elevation for a patient whose E.S.R. was normally 2 mm./hr. However, in the majority of instances, the "normal" reading for a given individual who has rheumatoid arthritis cannot be known. It seemed possible that the diphenylamine test might be a more sensitive indication of rheumatic activity than the E.S.R., and, hence, of value in the study of patients who fall into the above group. This has not been so in the small number of cases studied by us.

The fluctuations of the diphenylamine level in some patients under steroid therapy were not reflected by similar fluctuations of the E.S.R. This seems to be a further disadvantage of the test considered as a practical measure, but is of some theoretical interest. We have no explanation for these fluctuations, but further investigations might be rewarding.

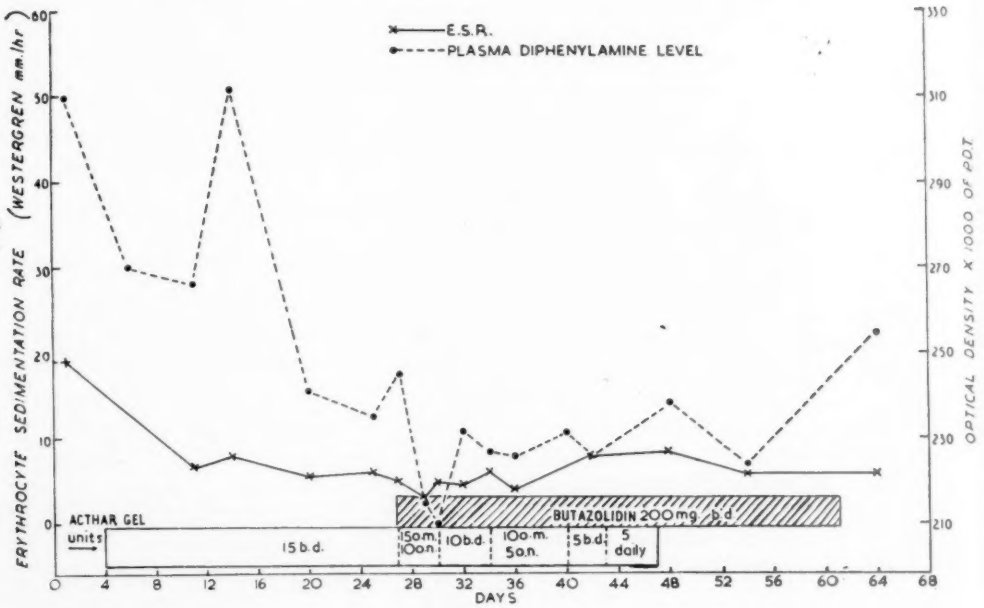

Fig. 4.—Results in a female patient aged 31.

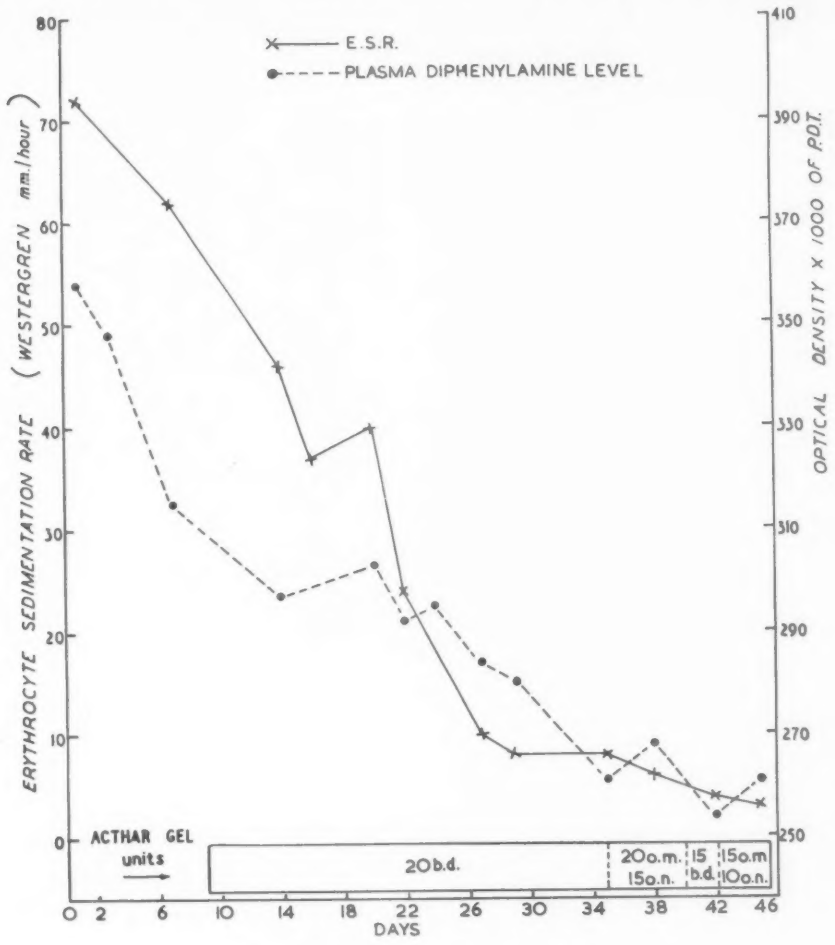

Fig. 5.—Results in a male patient aged 21.

In conclusion, we would emphasize that any test of rheumatic activity must be shown to have some advantage over the E.S.R. before it can be recommended as a practical measure.

Summary

(1) The diphenylamine reaction has been investigated as a measure of activity in rheumatoid arthritis and has been compared with the erythrocyte sedimentation rate with which it correlates, but over which it seems to have no particular advantage.

(2) The diphenylamine level fell in patients undergoing steroid therapy, but in some patients there were unexplained fluctuations, not reflected by the erythrocyte sedimentation rate.

(3) In patients with clinically active rheumatoid arthritis but with normal erythrocyte sedimentation rates, the diphenylamine reaction was not of much value as an indication of activity.

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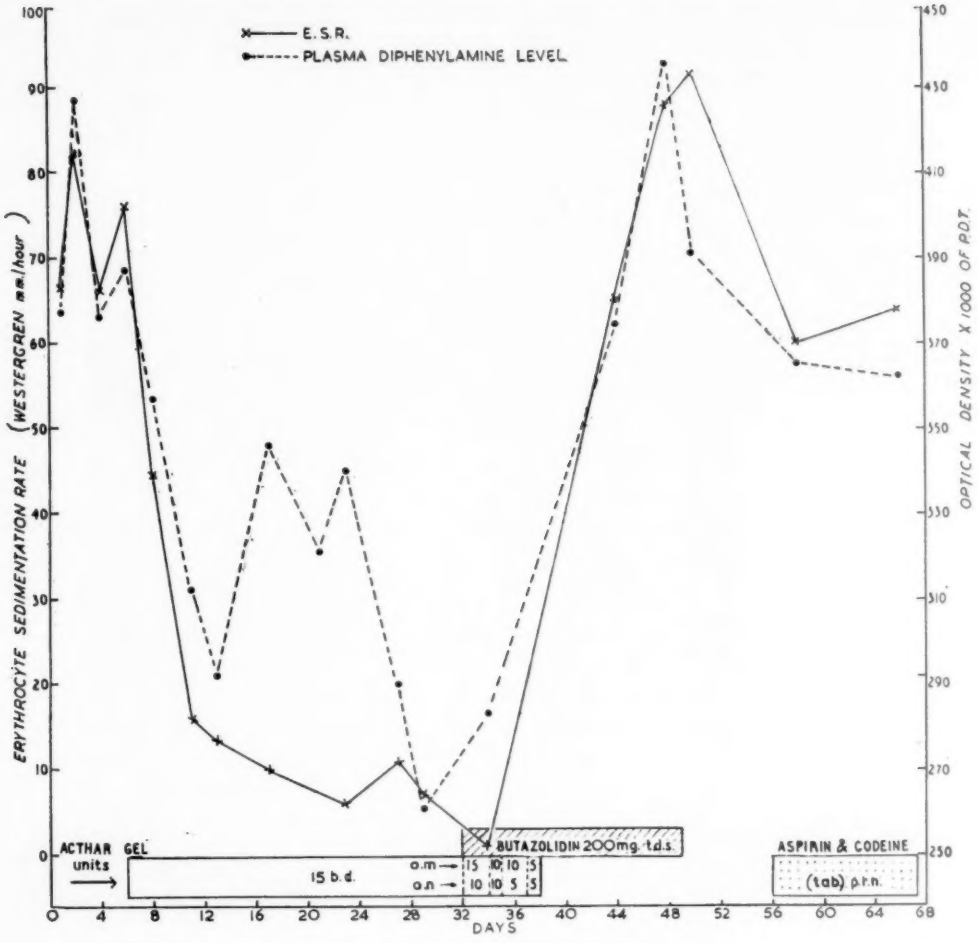

Fig. 6.—Results in a female patient aged 65.

La réaction de diphénylamine dans l'arthrite rhumatismale

RÉSUMÉ

(1) On étudia la réaction de diphénylamine comme mesure d'activité de l'arthrite rhumatismale et on la compara à la vitesse de sédimentation globulaire à laquelle elle est liée, sans lui être supérieure d'une manière quelconque.

(2) Le taux de diphénylamine chez des malades soumis à la thérapie stéroïde baissait, mais chez certains d'entre eux il y avait des fluctuations inexplicables qui ne correspondaient pas à la vitesse de sédimentation globulaire.

(3) Chez des malades atteints d'arthrite rhumatismale cliniquement active avec une sédimentation normale, la réaction de diphénylamine comme indicatrice d'activité était peu utile.

La reacción de difenilamina en la artritis reumatoide

SUMARIO

(1) Se estudió la reacción de difenilamina como medida de actividad de la artritis reumatoide y se la comparó a la velocidad de sedimentación eritrocitaria a la cual esta reacción está ligada, sin superarla de manera alguna.

(2) La cifra de difenilamina bajó en enfermos sometidos a la terapia esteroide pero en algunos hubo fluctuaciones inexplicables que no correspondieron a la velocidad de sedimentación eritrocitaria.

(3) En enfermos con artritis reumatoide activa y con velocidad de sedimentación eritrocitaria normal, la reacción de difenilamina fué de poca utilidad para indicar la actividad.

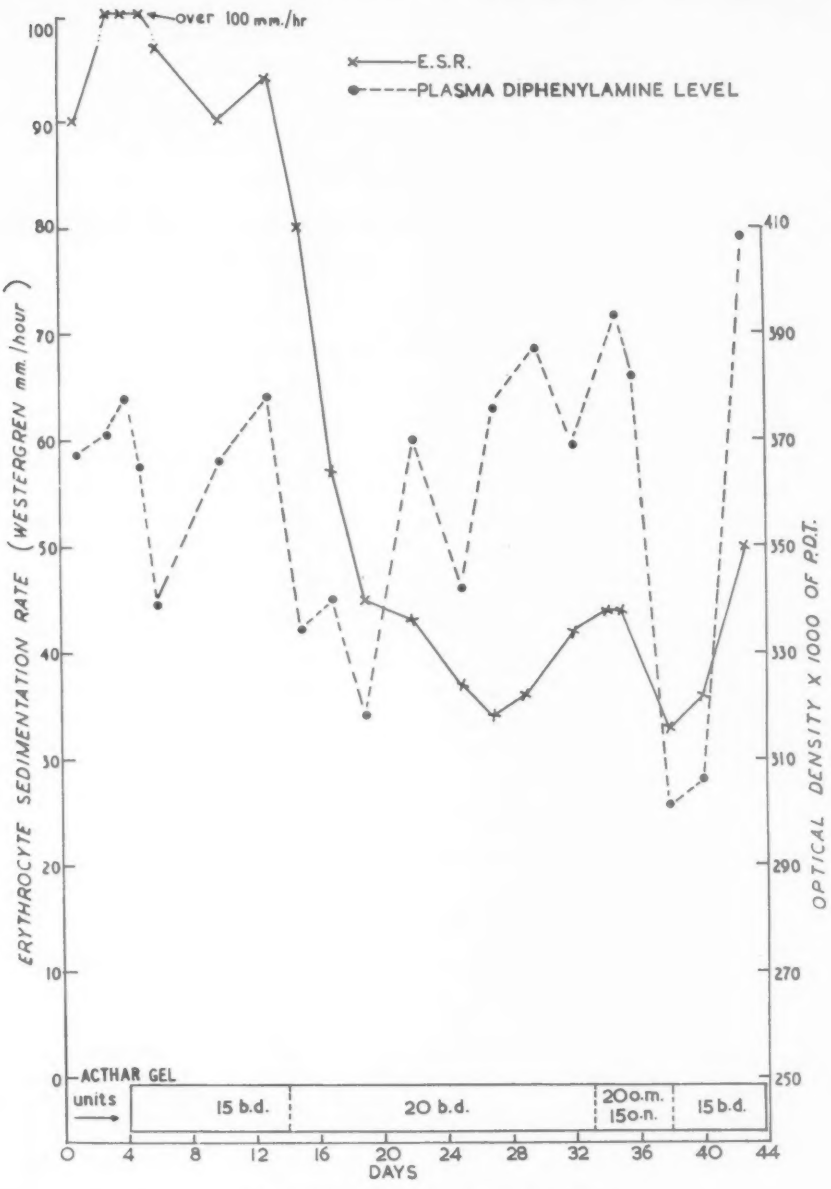

Fig. 7.—Results in a male patient aged 38.

Ann. rheum. Dis. (1955), **14**, 232.

ORAL HYDROCORTISONE THERAPY IN RHEUMATOID ARTHRITIS

AN APPRAISAL OF GENERAL RESULTS OF PROLONGED ADMINISTRATION

BY

EDWARD W. BOLAND

Los Angeles, California

(RECEIVED FOR PUBLICATION JUNE 6, 1955)

When hydrocortisone was made available for clinical trials in the spring of 1951, three facts seemed relevant:

(1) The hormone was the principal, probably the natural, glycogenic steroid secreted by the adrenal cortex (Hechter, 1950; Hechter and others, 1951; Reich and others, 1950; Savard and others, 1952; Bush, 1951; Conn and others, 1951; Jacobsen and Pincus, 1951; Pincus, 1949; Mason, 1950).

(2) It was considerably more potent than cortisone in certain metabolic activities, as measured by laboratory experiments in animals (Ingle and Kuizenga, 1945; Pabst and others, 1947).

(3) It possessed antirheumatic activity, this having been demonstrated by Hench, Kendall, Slocumb, and Polley (1950) in a rheumatoid arthritic patient given 900 mg. of the substance over a 12-day period.

During 1951 and 1952 clinical studies were conducted to compare the therapeutic effectiveness of hydrocortisone and cortisone in patients with rheumatoid arthritis (Boland, 1952a, b, c, d; 1953a, b; 1954; Boland and Headley, 1952).

The general results of these studies may be summarized as follows:

(1) The pattern of improvement resulting from the administration of the two steroids was much the same, but smaller initial suppressive doses of hydrocortisone were required to produce corresponding inhibition of the disease manifestations.

(2) By comparing the effects of oral doses in the same patient, the antirheumatic potency of hydrocortisone was estimated to be about 50 per cent. greater than that of cortisone acetate or its free ester. In other words, the average milligram dosage of hydrocortisone needed for roughly the same degree of improvement was approximately two-thirds that of cortisone.

(3) Smaller maintenance doses of hydrocortisone were found to provide equal or superior rheumatic control, and when these were used, certain endocrine complications appeared to be fewer or less pronounced, especially psychic stimulation, salt-and-water retention, and excessive appetite.

These preliminary observations suggested that there might be a greater dissociation between the desirable anti-inflammatory action and certain undesirable physiological effects with hydrocortisone than with cortisone, and that hydrocortisone might possess a higher therapeutic index—*i.e.* it might provide equal or greater benefits with smaller doses and fewer or less marked untoward reactions.

Subsequently a study of the effects of oral hydrocortisone given uninterruptedly was undertaken in a large series of patients with rheumatoid arthritis, the relatively short-term results of which have been published (Boland, 1953b; 1954). It now seems opportune, particularly since new synthetic analogues of the adrenocortical hormones have been discovered, to record the results of longer-term observations.

Present Analysis

For this report the results of prolonged oral hydrocortisone therapy* in 150 consecutive patients with active peripheral rheumatoid arthritis were analysed. As statistical results are necessarily contingent on a number of factors (including the composition of the series in relation to disease severity and duration, therapeutic plan and objective, method of dosage regulation, opinion as to what constitutes satisfactory response, and judgment as to the acceptability and safety of hormonal complications), some of these aspects, as applied to the present study, deserve clarification.

Each patient selected for the study first had been given a fair but unsuccessful trial on conventional conservative measures. The majority of the patients suffered from more severe forms of the disease; the arthritis was graded as severe in 39 patients (26 per cent.), moderately severe in seventy (47 per

* The hydrocortisone (free alcohol) used for this investigation was supplied in part through the courtesy of the Medical Department, Merck and Co., Inc., Rahway, N.J.

cent.), and moderate in 41 (27 per cent.). No patients with mild disease were included.

The guiding therapeutic policy was to maintain as much relief as possible with doses of hydrocortisone which could be well tolerated. Complete inhibition of the disease manifestations and total functional rehabilitation were not sought unless these could be accomplished with so-called safe levels of dosage. Submaximal improvement of about 75 to 85 per cent. of the pretreatment status was considered optimal for long-term administration. This policy was adopted because it was recognized that benefits from the hormone were only suppressive, not curative, and it had been learned from previous experience with cortisone that the incidence and severity of hormonal complications were directly related to the size of dose employed, and that their occurrence was a major factor influencing the success of long-term therapy.

Adequate or major improvement by our appraisals meant very marked or marked, and corresponded to overall improvement of approximately 75 per cent. or more as compared with the pretreatment status. It should be emphasized that improvement designated as inadequate was at least worthwhile or treatment would have been discontinued.

The following plan of dosage, consisting of three stages, was used:

(*a*) *Initial Suppressive Doses.*—As a rule, total daily dosages in the neighbourhood of the following were employed at the beginning: for severe cases, 50 to 70 mg.; for moderately severe cases, 40 to 60 mg.; for moderate cases, 40 to 50 mg. These amounts were continued until the clinical manifestations were satisfactorily suppressed, ordinarily for one to three weeks.

(*b*) *Reduction of Dosage.*—Dosage was then gradually lowered in stepdown fashion, reductions of 5 mg. being made every 7 to 14 days, or sometimes even more slowly. The smallest total daily amount which would control the manifestations adequately, not necessarily completely, and which could be safely tolerated, was considered as the maintenance dose.

(*c*) *Maintenance Dosage.*—Maintenance doses ordinarily ranged from 45 to 65 mg. in severe cases, 40 to 50 mg. in moderately severe cases, and 25 to 40 mg. in moderate cases. Once established, maintenance therapy was continued without interruption, the dosage being manipulated from time to time to accommodate shifts in disease activity or to control adverse reactions. Routinely the total daily requirement was taken in four divided doses, with a portion ingested at mealtimes and at bedtime. Dosage adjustments were usually made by small increases or decreases of 5 or 10 mg. at a time; large "booster" doses were rarely needed.

Minor endocrine side-effects, such as slight to moderate facial mooning or hypertrichosis, slight peripheral oedema, or irregular glycosuria, were usually looked upon as acceptable annoyances and not as reasons for stopping treatment.

Adjunctive measures such as regulated rest, avoidance of emotional stress, physiotherapy, and a well-balanced diet, relatively low in salt and with caloric restriction when indicated, were prescribed simultaneously. Salicylates were used regularly or irregularly by some patients and intra-articular injections of hydrocortisone acetate were occasionally employed in others to suppress exacerbations in one or two joints.

General Results

Statistical data were analysed in the hope of finding answers to a few general but pertinent questions:

(1) *What percentage of patients who were started on hydrocortisone therapy discontinued the hormone and for what reasons?* The 150 patients in this study were under observation for periods of 9 to 36 months from the beginning of therapy; more than one-third of them (37 per cent.) were followed for 2 years or longer. Treatment was stopped in 24 patients (16 per cent.), and the remaining 126 (84 per cent.) were still taking the steroid at the time of analysis. Reasons for discontinuances were as follows:

Insufficient clinical response to warrant further administration in four (2·7 per cent.),
Major complications attributable to the hormone in two (1·3 per cent.),
Complication unrelated to hydrocortisone in one (0·7 per cent.),
Death from extraneous causes in five (3·3 per cent.),
Complete or nearly complete remission in twelve (8 per cent.) patients (Table).

TABLE

GENERAL DATA ON 150 CONSECUTIVE RHEUMATOID ARTHRITIC PATIENTS STARTED ON HYDROCORTISONE THERAPY (ANALYSIS 9 TO 36 MONTHS AFTER INSTITUTION OF THERAPY)

	No.	%
Patients still on Therapy	126	84
Therapy discontinued	24	16
Reasons for discontinuing Therapy:		
1. Insufficient Clinical Result	4	2·7
2. Major Complication from Hydrocortisone	2	1·3
3. Death from Causes Unrelated to Hydrocortisone	5	3·3
4. Complication Unrelated to Hydrocortisone	1	0·7
5. Disease Remission	12	8
Complete	9	6
Partial	3	2

(2) *What overall results may be achieved from prolonged hydrocortisone therapy?* At the time of analysis, improvement was considered to be adequate or satisfactory in 59per cent. of patients and

less than satisfactory in 41 per cent. Inadequate degrees of improvement were noted in 62 patients for one or more reasons:

37 (62 per cent.) failed to respond satisfactorily to reasonable sized doses from the beginning of treatment,

Thirteen (22 per cent.) were controlled well at first, but later improvement deteriorated and responsiveness to the hormone diminished,

37 (62 per cent.) developed hormonal side-reactions which prohibited the use of optimally effective doses,

Five (8 per cent.) presented miscellaneous other reasons for limited improvement.

Female patients fared almost as well as male patients: inadequate improvement was recorded in 42 per cent. of the former and in 39 per cent. of the latter.

(3) *What are the chief factors which influence the success of therapy?* Apart from recognized correctible mistakes in management (*i.e.* poor selection of patients, inadequate supervision, improper dosage regulation, neglect of appropriate rest, and simple complemental measures such as avoidance of trauma, etc.), which may lead to failure, it was apparent from this study that therapeutic results bore important relationship to two factors—the severity or activity of the disease and the duration of arthritis before treatment.

At the time of analysis improvement was graded as adequate in 36 per cent. of patients with severe, 57 per cent. of patients with moderately severe, and 88 per cent. of patients with moderate disease (Fig. 1). In general, the same problem pertained as with cortisone: for satisfactory control the more severe cases all too often required excessive doses which could not be tolerated or which were considered unsafe for long-term administration. Surely, statistical results would have been more favourable had the series contained a larger percentage of moderate and some mild cases. As might be expected, the remission rate was greater in patients with moderate disease (14·5 per cent.) than in those whose arthritis was moderately severe (7·1 per cent.) or severe (0·025 per cent.).

Percentagewise, results were most favourable when the arthritis was of relatively recent origin. Interestingly, the crucial point was about 2 years, and thereafter as the duration of disease lengthened, the proportion of adequate responses lessened progressively (Fig. 2). Not surprising was the finding that the remission rate was decidedly lower in patients whose disease had been established more than 2 years (4 per cent.) than when the duration was 2 years or less (22 per cent.).

(4) *What deterioration of improvement may be expected as treatment is prolonged?* Analyses made at intervals during the

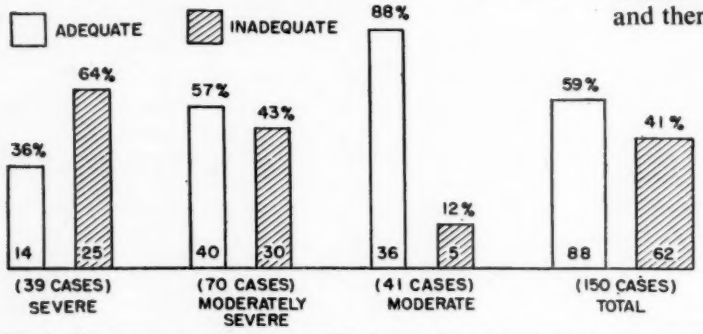

Fig. 1.—Improvement on adequate and inadequate dosage in relation to severity of disease.

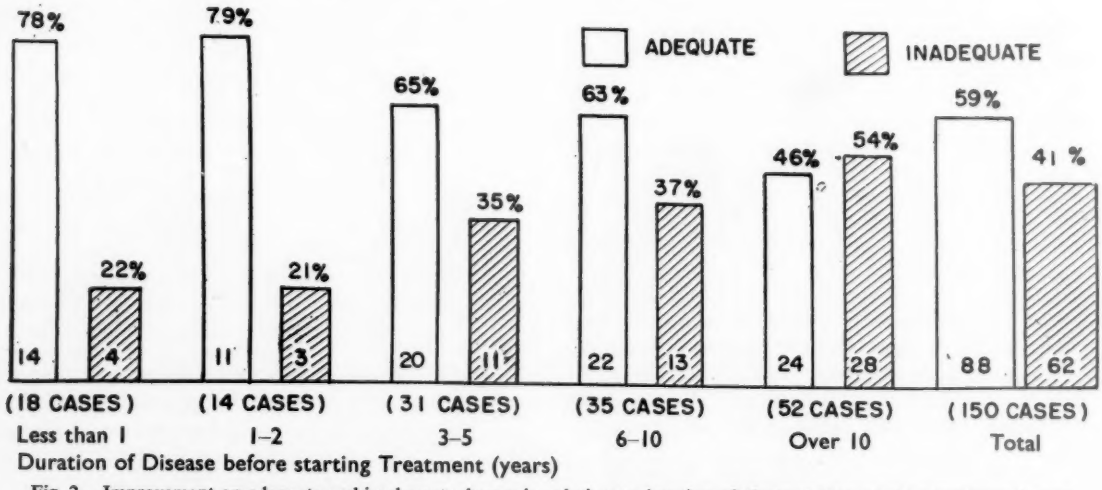

Fig. 2.—Improvement on adequate and inadequate dosage in relation to duration of disease before starting treatment (years).

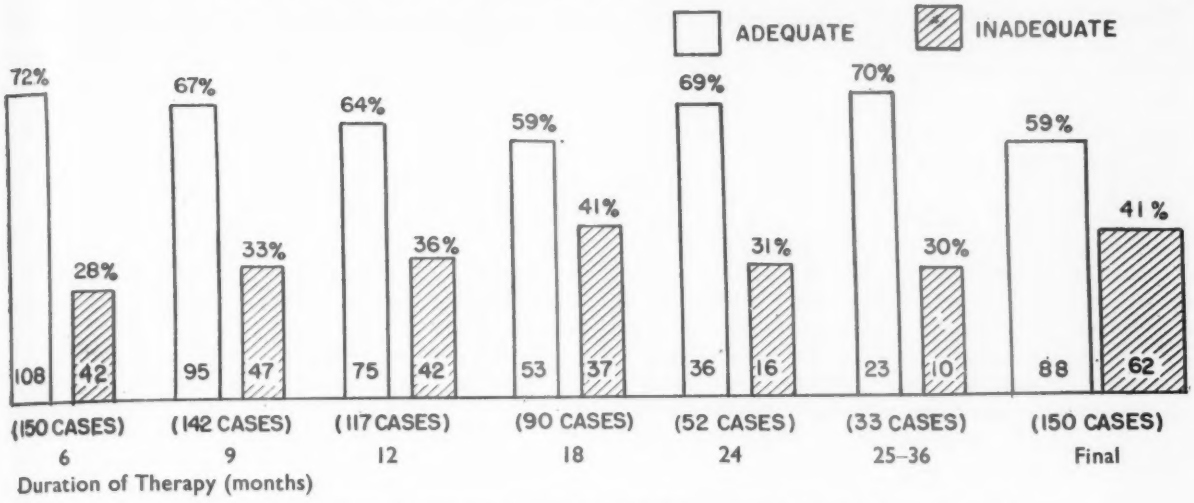

Fig. 3.—Improvement on adequate and inadequate dosage in relation to duration of therapy (months).

period of observation revealed, as anticipated, that as treatment was continued over the months, the number of patients showing adequate improvement became smaller. The figures (Fig. 3) may be confusing unless it is understood that patients were added to the series as the study progressed and that others were dropped from time to time because of remission, insufficient benefit, or other reasons. The disease was satisfactorily restrained in 72 per cent. of patients at the end of 6 months, but this percentage declined to 59 per cent. at 18 months. At 24 months and later the number demonstrating satisfactory control rose to around 70 per cent.; this is explained by the fact that the majority of patients who became unresponsive or developed unacceptable complications discontinued the hormone within a 2-year period.

(5) *What influence does long-term hydrocortisone therapy have on the progress of the disease?* Among the 150 patients, fifty (33 per cent.) showed evidence of disease progression during the observation period. Functional capacity was altered significantly by advancement of the arthritis in 31 patients but not in the nineteen others. The ability of steroid therapy to restrain disease progress varied indirectly with the severity or activity of the rheumatoid arthritis. Clinical evidences of progression were noted in 44 per cent. of severe cases, 34 per cent. of moderately severe cases, and 22 per cent. of moderate cases (Fig. 4). An unexpected finding in patients of this series was a lack of correlation between the frequency of disease progression and the duration of the arthritis before therapy (Fig. 5).

It is impossible to judge with full assurance what influence hydrocortisone therapy may have exerted on the natural course of the disease. There are no statistical data available with which to compare the incidence or rate of disease progression in

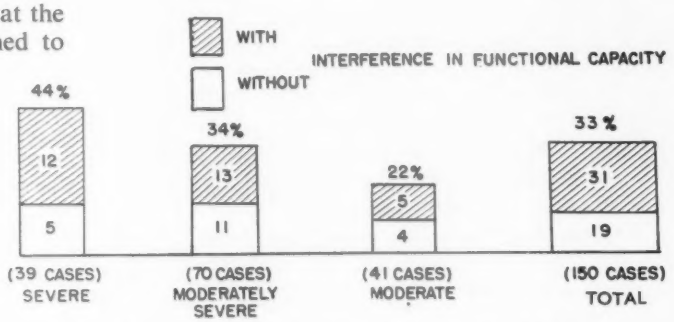

Fig. 4.—Disease progression in relation to severity of disease.

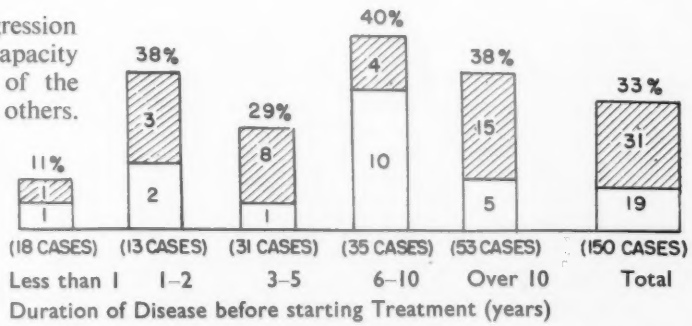

Fig. 5.—Disease progression in relation to duration of disease before starting treatment (years).

untreated or conservatively treated patients in a series of similar composition. Furthermore, the periods of observation in the present study were relatively short (9 to 36 months) in respect to the average span of the disease. However, when consideration is given to the facts that the majority of patients (73 per cent.) suffered from severe or moderately severe forms of rheumatoid arthritis and that they had already failed to respond satisfactorily to conservative management, the incidence of disease progression seems smaller than might have been expected for a similar untreated series. The impression was gained that in cases amenable to hydrocortisone, advancement of the rheumatoid process may frequently be retarded during the period of steroid administration, and perhaps more frequently than heretofore considered.

(6) *How satisfactory is hydrocortisone as a long-term treatment agent for rheumatoid arthritis?* Orally administered, hydrocortisone must be regarded as a very valuable agent in the management of selected cases of rheumatoid arthritis. It promotes a high rate of immediate therapeutic response and, with relatively low maintenance doses, it is capable of providing continuous, adequate control of the rheumatic manifestations in a significant percentage of cases. Nearly 60 per cent. of patients in the present series, whose arthritis was unsuccessfully regulated by measures other than steroid therapy, were held in major improvement by the drug during observation periods ranging from 9 to 36 months. Though benefits were less than desired, varying amounts of helpful relief and enhanced functional capacity were furnished to many patients in the remaining 40 per cent.

Nevertheless, hydrocortisone is far from an ideal therapeutic agent for rheumatoid arthritis. Apart from its main deficiency, that of having suppressive rather than curative action, it has, like cortisone, many serious shortcomings. Among these may be listed:

(1) The intervention of hormonal side-effects which serve to limit dosage and often satisfactory management, especially in patients with more severe or long-established disease whose daily requirements for the drug are large;
(2) The tendency to aggravate certain co-existing pathological conditions, which contra-indicate its use;
(3) The decrease in responsiveness and improvement in some patients after prolonged administration;
(4) The frequent failure of the hormone to prevent progression of the disease during treatment.

Thus, until a cure for rheumatoid arthritis is found, there is need for an agent which, on systemic administration, will suppress the disease more successfully over long periods and in a higher proportion of patients. A steroid with wide disparity between its anti-inflammatory power and its tendency to produce unwanted effects would partially fulfil this need. That it may be possible to prepare such compounds is suggested by a number of encouraging new developments, which have shown that modifications in the chemical structures of hydrocortisone and cortisone may attenuate those physiological actions which lead to troublesome complications.

Summary

The results of prolonged oral hydrocortisone therapy (9 to 36 months) in 150 consecutive patients with active peripheral rheumatoid arthritis were analysed. The following pertinent statistical information was derived:

(1) At the time of analysis, treatment with the hormone had been discontinued in 24 patients (16 per cent.) for the following reasons: insufficient clinical response in four (2·7 per cent.); major complications in two (1·3 per cent.); complications unrelated to hydrocortisone in one (0·7 per cent.); death from extraneous causes in five (3·3 per cent.); remission in twelve (8·0 per cent.).

(2) Improvement was considered as adequate in 59 per cent. of patients and less than satisfactory in 41 per cent. at the time of analysis.

(3) The chief factors which influenced the success of therapy were the severity or activity of the disease and the duration of arthritis before treatment. At analysis, improvement was graded as adequate in 36 per cent. with severe disease, 57 per cent. with moderately severe disease, and 88 per cent. with moderate disease. Results were more favourable when the arthritis was of relatively recent origin; the crucial duration was about 2 years, and thereafter as duration lengthened the proportion of adequate response lessened.

(4) As time went on, fewer patients showed adequate improvement. The disease was restrained satisfactorily in 72 per cent. at 6 months and in 59 per cent. at 18 months.

(5) Fifty of the 150 patients (33 per cent.) showed evidence of disease progression during the observation period. Functional capacity was not reduced significantly by advancement of the arthritis in 19 of them, but was altered in the remaining 31 patients.

The following conclusions were drawn:

Although hydrocortisone is a very valuable agent in the management of selected cases of rheumatoid arthritis, it is far from an ideal suppressive agent. Like cortisone, it has many shortcomings, chief among which are the intervention of hormonal side-effects, especially when dosage requirements are large; the tendency to aggravate certain co-existing pathological conditions; the development of unresponsiveness in some patients after prolonged administration; the failure to prevent disease progression in an appreciable percentage of cases.

Thus, until a cure for rheumatoid arthritis is found, there is still need for an agent which will suppress the disease more successfully. That such a compound may be forthcoming is suggested by recent discoveries of steroids related to hydrocortisone and cortisone which possess wider dissociation the anti-inflammatory properties and the other unwanted physiological activities.

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Hydrocortisone par voie buccale dans l'arthrite rhumatismale

RÉSUMÉ

On analysa les résultats du traitement prolongé (9 à 36 mois) à l'hydrocortisone par voie buccale de 150 malades consécutifs atteints d'arthrite rhumatismale périphérique. On obtint des données statistiques pertinentes que voici:

(1) Au temps de l'enquête, le traitement à l'hormone se trouvait interrompu chez 24 malades (16%) pour des raisons suivantes: réponse clinique insuffisante 4 (2·7%); complications majeures 2 (1·3%); complications indépendantes de l'hydrocortisone 1 (0·7%); morts de causes différentes 5 (3·3%); remission 12 (8%).

(2) A l'heure de l'enquête, l'amélioration fut considérée satisfaisante chez 59% des malades et moins que satisfaisante chez 41%.

(3) L'issue du traitement dépendait de deux facteurs principaux: la sévérité ou bien l'activité de la maladie et la durée de l'arthrite avant le traitement. A l'enquête on a classé 36% des malades graves, 57% des assez graves et 88% des modérement atteints parmi les améliorés d'une manière satisfaisante. Les résultats ont été plus favorables dans l'arthrite relativement récente, avec une durée critique de deux ans à peu près, après quoi la proportion des améliorations satisfaisantes diminuait au fur et à mesure que l'ancienneté de l'arthrite augmentait.

(4) Avec le temps, le nombre d'améliorations satisfaisantes diminuait. La maladie se trouvait jugulée dans 72% des cas au bout de 6 mois et dans 59% des cas seulement au bout de 18 mois.

(5) Chez 50 (33%) malades sur 150 au cours de la période sous observation on a noté des signes d'évolution de la maladie. Chez 19 d'entre eux l'aggravation de l'arthrite n'a pas entrainé de réduction appréciable de la capacité fonctionnelle, mais elle l'a altéré chez les 31 restants.

On tire des conclusions suivantes:

Bien que l'hydrocortisone soit un moyen très utile dans le traitement des cas determinés d'arthrite rhumatismale, elle est loin d'être un agent idéal de suppression. Comme la cortisone, elle a ses défauts dont le principal est le pouvoir de provoquer des réactions endocrines secondaires, surtout lorsqu'on doit administrer des doses élevées; elle tend à aggraver certains états morbides coexistants; certains malades cessant à répondre à son administration prolongée et dans un nombre appréciable des cas elle n'arrive pas à arrêter l'évolution de la maladie.

Il s'en suit, qu'à moins qu'on trouve une cure, on aura toujours besoin d'un moyen plus satisfaisant pour juguler l'arthrite rhumatismale. La découverte récente des stéroïdes apparentés à l'hydrocortisone et à la cortisone, dans lesquels le pouvoir anti-inflammatoire et certaines propriétés physiologiques indésirables se trouvent plus dissociés, semble indiquer qu'un tel moyen ne se fera pas attendre.

Hidrocortisona por vía oral en la artritis reumatoide

SUMARIO

Se analizaron los resultados de tratamiento prolongado (9 a 36 meses) con hidrocortisona por vía oral de 150 enfermos consecutivos con artritis reumatoide perifèrica. Los siguientes datos estadísticos pertinentes fueron obtenidos:

(1) Al tiempo del análisis, en 24 enfermos (16%) se dejó el tratamiento hormonal por razones siguientes: respuesta clínica inadecuada, 4 (2·7%); complicaciones mayores, 2 (1·3%); complicaciones independientes de la hidrocortisona, uno (0·7%); muertos de causas ajenas, 5 (3·3%); remisión, 12 (8%).

(2) Al tiempo del análisis, la mejoría se juzgó satisfactoria en el 59% de los enfermos y poco satisfactoria en los demás 41%.

(3) El éxito del tratamiento dependió de dos factores principales: la severidad o la actividad de la enfermedad y la duración de la artritis antes del tratamiento. En el análisis el 36% de los enfermos graves, el 57% de los bastante graves y el 88% de los moderados fueron clasificados como satisfactoriamente mejorados. Los resultados fueron mejores en la artritis relativamente reciente, con duración crítica de dos años aproximadamente; luego, la proporción de las mejorías satisfactorias bajaba a medida que la antigüedad de la artritis aumentaba.

(4) El número de las mejorías satisfactorias disminuía con el tiempo. La enfermedad estaba contenida en un 72% de los casos a cabo de seis meses y en un 59% solamente después de dieciocho meses.

(5) Durante el período de observación se notaron signos de evolution en 50 de los 150 enfermos. En 19 de ellos la agravación de la artritis no fué seguida de reducción apreciable de la capacidad funcional, alterada en los demás 31.

Se llegó a las conclusiones siguientes:

Aunque la hidrocortisona sea un medio muy útil en el tratamiento de casos determinados de artritis reumatoide, le falta mucho para ser un agente represivo ideal. Como la cortisona, tiene sus defectos entre los cuales se destaca su propiedead de causar reacciones hormonales secundarias, en particular cuando se necesitan dosis elevadas; su tendencia a agravar ciertas afecciones coexistentes; algunas enfermedades dejan de responder a su administración prolongada y, en un número apreciable de casos, no llega a contener la evolución mórbida.

Así pués, a menos de hallar una cura, un medio más satisfactorio para contener la artritis reumatoide aún nos hace falta. La reciente descubierta de esteroides relacionados con la hidrocortisona y la cortisona, en los cuales el poder anti-inflamatorio y ciertas propiedades fisiológicas indeseables están disociadas parece indicar que la descubierta de un tal medio no está lejos.

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A SHORT REVIEW OF CONNECTIVE TISSUE METABOLISM

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Our knowledge of connective tissue metabolism is mostly very new and can at present only be gleaned from widely scattered publications. An incomplete account of collagen metabolism is included in a recent symposium edited by Asboe-Hansen (1954), and there are fuller reviews of mucopolysaccharide metabolism. But these accounts do not, naturally enough, consider some important and more recent information. It would, therefore, seem useful to attempt to review the present position. It has not been for want of interest that the dynamics of connective tissue should only now be receiving attention. After all, connective tissue histology is of almost venerable antiquity, and there were the earlier metabolic studies, such as that of Bywaters (1937), to show that adult connective tissue has a negligible oxygen consumption and therefore, presumably, a low metabolic activity. But two main difficulties stood in the way of biochemical progress. First, the lack of a satisfactory method of investigation, and, secondly, the difficulties inherent in separating and chemically characterizing adequate amounts of material for such studies. The first difficulty has been resolved by the more general availability of radioactive isotopes, and by rapid progress in methods of using them as tracer substances in following the progress of metabolic change. The second difficulty is still with us, and a formidable amount of work still remains to be done in devising methods of separating the connective tissue components in forms which are not grossly altered from their state in the living body, and in their chemical characterization.

Metabolism of Collagen and Elastin in the Normal Animal

(1) Collagen Fibres: "Mature" Collagen.—Rat tendon collagen metabolizes more rapidly in the young than in the old, judged by the gain and loss of isotopic glycine; its turnover is lower than that of collagen from elsewhere, and that of collagen is lower than that of other tissues (Neuberger and others, 1951; 1953).

Results have also been reported indicating a relatively slow rate of turnover of collagen in guinea-pigs (Robertson, 1952).

(2) Soluble Collagens and Precursors of Collagen.—The foregoing experiments used methods of extraction and purification of collagen which resulted in an end-product almost wholly derived from fully-formed "mature" collagen fibres. Only in the very young animals is the collagen likely to have included some soluble or "immature" collagen, and the possible inclusion of some precursor collagen in the final extract might account for the small but definite metabolic activity of the collagens in the young rats. The possibility that collagen changes in its metabolic behaviour with increasing age of the animal is suggested by physical differences observed in collagen obtained from young and old animals' tendons (Jordan-Lloyd and Marriott, 1935; Leplat, 1935). The existence of soluble, collagen-like proteins in connective tissue has been known for quite a long time and appears to have been first reported by Zachariadès (1900). The dissolution of collagen in very dilute acetic acid, especially that of the tail tendon of the rat, was studied in detail by other French workers, particularly by Nageotte, in the late 1920s and 1930s. Only a small part of the collagen goes into solution normally in dilute acetic acid, and it is interesting to note that the proportion of collagen which so dissolves was found to decrease with age (Nageotte and Guyon, 1934). More recently, Russian workers, especially Orekhovitch and his co-workers have studied the properties and distribution of soluble collagen in a

great variety of species and tissues. The material studied by Orekhovitch (1950) and Orekhovitch and others (1948) appears to be identical with that described by the earlier French workers. Orekhovitch called this soluble protein "procollagen", implying that it is a precursor of insoluble collagen; it occurs in relatively large amounts only in connective tissue of young animals. The presence of another type of soluble collagen was suggested by the work of Highberger, Gross, and Schmitt (1951), who found that an extract of skin made with slightly alkaline phosphate solutions contained a protein which in its appearance under the electron microscope resembled collagen. It was obviously of great importance to attempt to determine whether soluble collagens were the precursors of "mature" fully-formed collagen fibres.

An attempt to elucidate this problem was made by Harkness, Marko, Muir, and Neuberger (1954), who studied the incorporation of labelled glycine into soluble collagens extracted from the skin of very young rabbits. Several points arise from this important work. By extraction procedures three forms of collagen can be distinguished. The first, alkali-soluble collagen, is initially soluble in disodium hydrogen phosphate solutions. The second, acid-soluble collagen, is extracted by acidic buffers such as citrate *p*H 4. This is identical with the "procollagen" of Orekhovitch and corresponds to the soluble collagen of the earlier French workers. Finally, there is the insoluble or "mature" collagen which remains after repeated phosphate and citrate extractions. Very marked differences were observed in the incorporation of labelled glycine into these three collagen fractions, and these differences are illustrated in Fig. 1. The activity of the alkali-soluble collagen rises very rapidly to a high value in the first 24 hrs after isotope administration, and then falls sharply, so that at 3 days it is no higher than that of the insoluble collagen. In some of the experiments the activities observed in alkali-soluble collagen exceeded those found in any other protein, not excluding the plasma proteins. The rate of turnover of this collagen fraction is 2 days or less, and it seems very probable that this is the precursor of the collagen fibrils. The acid-soluble collagen, the so-called "procollagen", on the other hand shows very low activity by comparison. Also the activity of this fraction shows a slow rise in the first 3 days and at 7 days has fallen a little, so that it is about the same as the insoluble collagen. This kind of activity-time curve is not compatible with the assumption that acid-soluble collagen is a precursor of the collagen fibres. Finally, Fig. 1 shows that the activities observed in the insoluble collagen from these rabbit skins are very similar to the earlier experiments in rats, *i.e.* very low activities throughout with no appreciable loss of activity with time.

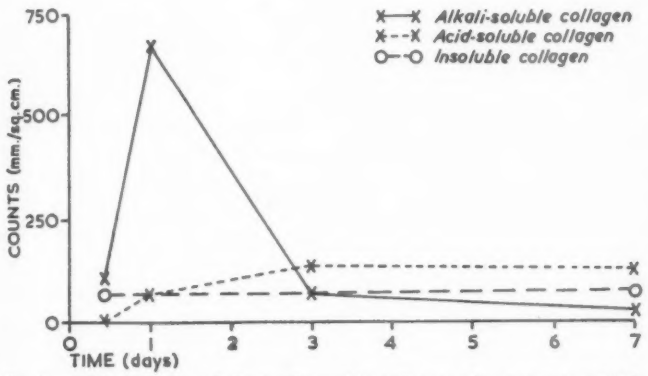

Fig. 1.—Radioactivities of glycine from skin collagens of very young rabbits fed [α-^{14}C] glycine by mouth. (See *Biochem. J.*, 1954, **56**, 558.)

(3) **Elastin.**—This important fibrous protein is a major constituent of the larger arteries and certain spinal ligaments. Although not unlike collagen in some respects, it differs in certain staining properties, in its appearance under the electron microscope and in its amino-acid pattern. It has been shown by Bowes and Kenten (1949) to contain less arginine, lysine, hydroxyproline, and glutanic acid, rather less aspartic acid, and more valine than does either collagen or reticular tissue. There is to date only one paper on its metabolism (Slack, 1954a). In these experiments normal adult rats were injected with [α-^{14}C] glycine, and killed, some 1 day, others 9 days later. Another group of rats with experimental atrophy of one hind limb were similarly treated. The aortae of the rats were dissected out, and the contained elastin was separated from other protein by first boiling under reflux for 4 days with 0·005 M acetic acid and then trypsinizing for 24 hrs at 37° C. and *p*H 8. The method has been shown by Tunbridge and others (1952) to free the elastin from associated collagen and give a satisfactorily homogeneous preparation for electron microscopy. The radio-activities of glycine recovered from the purified elastin were then determined. The observed radio-activities were essentially similar in both groups of rats at all time intervals and were of the same order as those found previously in bone collagen of adult rats. It therefore seems probable that in the adult rat elastin, in common with the major portion of collagen, has a very slow rate of turnover.

Changes in the Collagen Content of Tissues under Certain Physiological and Pathological Conditions

A number of histological investigations of the changes in the supporting elements of growing tissues have been done, but very few quantitative observations are reported on the chemical constituents of these supporting elements. Observations of this kind would provide valuable indirect information on connective tissue metabolism. Abercrombie and Johnson (1946) estimated collagen chemically in degenerating and regenerating nerve, and Harkness (1952) estimated collagen in liver regenerating after partial hepatectomy. In both instances collagen formation was found to be a slow process which lagged considerably behind changes in the principal cellular elements of the tissue. Similarly in cirrhosis of the liver produced by carbon tetrachloride quantitative estimation of collagen showed a slow increase (Morrione, 1949). In rats treated with thiouracil there was increase in weight of the thyroid gland and of its collagen content, but again the latter increase was slower than that of the total tissue (Harkness, Harkness, and Santler, 1954). More interesting was the observation that on cessation of thiouracil treatment there was a relatively quick removal of collagen from the gland.

Much more rapid formation of collagen has been observed in the uterus of the rat during pregnancy (Harkness and Harkness, 1952). The increase in collagen content in this instance closely parallels the increase in the total wet weight, and in the puerperium there is a very rapid fall in both total weight of the uterus and its collagen content. Under the physiological stimulus of pregnancy there is this great local increase in the rate of synthesis of collagen, followed by an equally spectacular increase in the rate of removal or reabsorption of collagen.

Massive removal or reabsorption of collagen has also been observed in experimental limb atrophy in the rat (Slack, 1954b). If one hind limb of the rat is immobilized by dislocation at the hip joint and avulsion of all main nerve trunks, then massive tissue wasting ensues in the limb. During the first 4 weeks after operation there is a fairly rapid loss of total wet weight followed by a long phase during which tissue wasting proceeds much more slowly. The loss of collagen from these wasting tissues of the limb follows a similar curve (Fig. 2). The rats were injected with [α-^{14}C] glycine and killed at various time intervals up to 15 weeks after operation. Collagen activities in the tissues of the normal hind limb and wasting hind limb were determined and it was found, rather surprisingly, that the specific activities of collagen from the two limbs were similar. Indeed, at 10 weeks onwards from operation, the collagen in the wasting limb showed somewhat higher activity than that from the normal control limb (Fig. 2). The experimental production of atrophy in a whole hind limb did not cause cessation of collagen synthesis, and the loss of collagen from the wasting tissues would appear to be due to increased activity of some at present unknown removal mechanism.

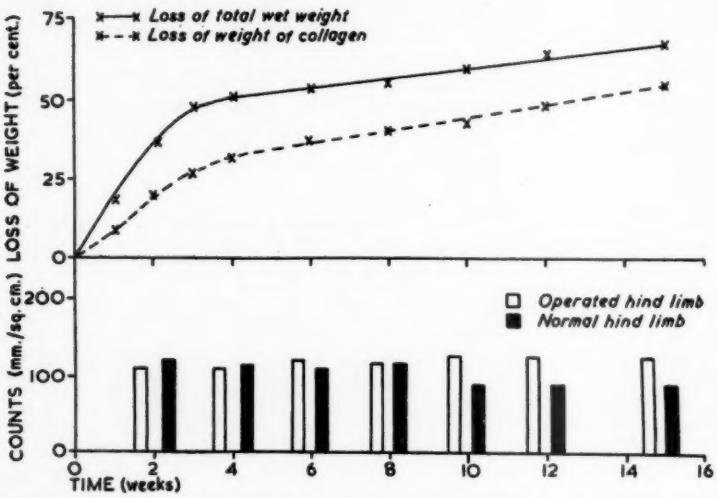

Fig. 2.—(*a*) Loss of total wet weight and loss of collagen (in g. per cent.) in experimental limb atrophy in adult rats.

(*b*) Specific activities of glycine from total collagen of operated and normal hind limbs of the same rats given [α-^{14}C] glycine and killed 2-15 weeks after operation. (See *Clin. Sci.*, 1954, **13**, 155.)

To summarize, in the normal animal the greater part of collagen is metabolically relatively inert. This is true at all ages, but it is almost certain that the proportion of total collagen which is in this state of inertia, metabolically speaking, increases with increasing age. In very young actively growing animals there is a substantial amount of collagen which is in a more soluble form. Some of this, forming only a small part of the total collagen even in very young animals, is the alkali-soluble collagen and this precursor is in a high state of metabolic activity. In adult tissues under normal conditions the amount of this alkali-soluble collagen must be very small indeed. But at least one important diversion from this metabolic pattern has been recorded. This is the rapid formation and equally rapid subsequent dissolution of collagen in the rat uterus in pregnancy. Information on the meta-

bolism of elastin is limited to one small series of experiments which suggest that its metabolic behaviour is similar to collagen. There is as yet no information whatever of the metabolism of the tyrosine-rich protein whose presence has been detected in bone, cartilage and skin, and which is probably present in other connective tissues.

Metabolism of Mucopolysaccharides

The substances with which we shall be concerned, here, are members of a group of high molecular weight polymers formed from glucosamine or galactosamine in combination with glucuronic acid and acetate, and which may contain ester sulphate. At present only two of these mucopolysaccharides are well characterized, hyaluronic acid and chondroitin sulphuric acid, and the greater part of metabolic studies have been concerned with these two substances. Heparin has been extensively investigated chemically, but nothing is yet known of its metabolism. There is a mounting weight of evidence indicating the presence in connective tissue of other mucopolysaccharides (*e.g.* Consden and Bird, 1954), but only one of these, chondroitin, has yet been adequately characterized (Davidson and Meyer, 1954). The separation and characterization of these mucopolysaccharide components of connective tissue is still at an early stage and the difficulties of the problem are increased by their close association in the tissues with protein.

That enzyme systems are involved in the sulphate exchange of cartilage chondroitin sulphuric acid has been demonstrated by Boström and Månsson (1953a). Labelled sulphate is taken up on incubating fresh costal cartilage slices *in vitro* at 37° C. Previous boiling prevents this uptake of ^{35}S and it is not shown by purified chondroitin sulphuric acid. The enzymatic exchange is inhibited by different kinds of enzyme inhibitors, especially -SH inhibitors, cortisone, and salicylic acid. A substance has been detected in liver homogenate which acts as a powerful stimulator of the sulphate exchange reaction (Boström and Månsson, 1953b). The active principle is thermo-stable and dialysable, but little else is known about it at present.

Dziewiatkowski (1949) showed that if a tracer dose of ^{35}S-labelled sulphate is given to an animal, most of it is rapidly excreted, only a small fraction being retained in the tissues. He also showed that there is a very high incorporation and relatively slow elimination of ^{35}S sulphate in cartilage, bone and bone marrow. Since this paper there have been numerous contributions using autoradiographic techniques to localize ^{35}S retained in the tissues. Most of these are *in vitro* studies, but tissue culture technique has also been used (Layton, Frankel, and Scapa, 1950). It is clear from this work that most of the retained ^{35}S is in the form of ester sulphate in the mucopolysaccharides of the connective tissues. Only a negligible amount occurs in other sulphur-containing components (Boström and Åqvist, 1952). A recent contribution to this field has been the study of the distribution of ^{35}S in fibrous tissues, cartilages and bones of the rat, after administration of ^{35}S-labelled sulphate, by Davies and Young (1954). They found the highest concentration of ^{35}S in the cell columns of epiphyseal cartilage. The labelled sulphate had disappeared from fibrous tissues and most cartilages, except the cell column zones, by the 10th day after injection. Four hours after injection some of the sulphate was in the inorganic form, the remainder was in a form insoluble either in distilled water or in buffer solution at *p*H 10. This fixed sulphate occurred principally in the pericellular zone and particularly in the region of the cartilage cell columns. Clearly this portion of the labelled sulphate has been incorporated into a component of the cartilaginous matrix. Furthermore, the fact that this fixed sulphate is in a form insoluble in buffer at *p*H 10 suggests that it is not simple chondroitin sulphate in free form, but is probably C.S.A. bound to protein in a form not readily dissociable. This interesting observation is confirmed by Shatton and Schubert (1954), who showed that chondroitin sulphuric acid existed in cartilage largely as a mucoprotein, or two electrophoretically similar mucoproteins. They also showed that the protein component was quite certainly not collagen but is a tyrosine-rich protein.

The rate of metabolism of chondroitin sulphuric acid in rats has been directly studied using ^{35}S-labelled sulphate (Boström, 1952; Boström and Gardell, 1953). They found a rate of turnover of 16 days for the C.S.A. from costal cartilage and of 10 days for the polysaccharide from skin. They considered the latter to be chondroitin sulphuric acid, but there is accumulating evidence (Consden and Bird, 1954) that the skin mucopolysaccharide is not a single substance, and the observed turnover rates are probably the means of several mucopolysaccharides with individual metabolic rates which may differ widely.

Also using ^{35}S-labelled sulphate, some experiments have been made to attempt to determine the turnover rates of mucopolysaccharides in normal rats and in rats with experimental limb atrophy (Slack, 1955). Very different rates of metabolism were found according to the method of extraction of the mucopolysaccharides. The rate of turnover

of cartilage chondroitin sulphate in normal rats was in agreement with that found by Boström, namely, 16 days. This was for a cartilage fraction separated by papain digestion. Total cartilage polysaccharide, after inorganic sulphate had been removed, showed a higher activity, and there appeared to be a residual sulphated mucopolysaccharide with a relatively long rate of turnover. The mucopolysaccharides from the limb tissues also varied considerably with the extraction procedure. In the operated limbs, with massive tissue wasting, there appeared to be an overall increase in mucopolysaccharide metabolism, but the general picture is still confused. Some preliminary separation of the limb tissue mucopolysaccharides has been achieved by ionophoresis in borate buffers. Three main mucopolysaccharide components have been found and the distribution of ^{35}S in these has been followed by scanning the electrophoretic bands after staining with Alcian blue. These quantities were then related to radioactivity by autoradiography of the bands, and also by elution and solid counting as $BaSO_4$ after hydrolysis. The ^{35}S appears to be distributed unevenly between these three mucopolysaccharides. Most of the activity appears to be distributed about equally between a slow moving and a fast moving component, but there is a third component of moderate speed in borate buffer *p*H 9·4 which is smaller in amount but is relatively highly labelled.

Experiments using ^{35}S-labelled sulphate have provided most of the available information on mucopolysaccharide metabolism. It is relatively cheap, readily available and not too difficult to work with, but it has some disadvantages. The most important of these is that any conclusions from such experiments must be confined to changes in the ester sulphate group, since it is possible that these changes may not be correlated with changes in other parts of the molecule.

It was with this drawback in mind that Schiller, Mathews, and Dorfman (1954) have recently introduced the use of ^{14}C-labelled acetate and glucose in this kind of experiment. Using starch ionophoresis they have perfected a method of isolating hyaluronic acid and a sulphated mucopolysaccharide from the skin of rabbits. The rate of incorporation of ^{14}C into the skin hyaluronic acid was found to be approximately three times as rapid as in the sulphated mucopolysaccharides, and the rate of decrease of activity was much greater in the hyaluronic acid. The rate of turnover of hyaluronic acid appears, from these experiments, to be very fast indeed, about 2 days. The sulphated polysaccharide had a turnover rate of about 9 days, being of the same order of magnitude as that reported earlier by Boström and Gardell (1953) using ^{35}S. Dorfman and others (1954) regarded the skin polysaccharide as a mixture, the observed turnover rate being probably the mean of several different rates. Further developments of this kind of experiment should provide more complete information about the metabolism of the mucopolysaccharide molecules.

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AGGLUTININS AND INCOMPLETE ANTIBODIES AFTER A SINGLE ANTIGENIC INOCULATION IN NORMAL AND RHEUMATIC INDIVIDUALS

BY

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It is well known that elevated levels of antibodies against various antigens of Group A pyogenic streptococci are found in rheumatic fever (Harris, 1948; Rantz and others, 1951). This phenomenon may be due to the increased immunologic reactivity of the macro-organism, to repeated natural infection by the micro-organism, or to the persistence of the micro-organism in the body of the host longer than in normal individuals. Several authors have already tried to establish that rheumatic subjects develop more antibodies than normal persons, even to antigens other than streptococcal.

Creger, Choy, and Rantz (1951) found that patients with diseases in which immunologic pathogenesis is presumed produce antibodies in higher titres than controls, but their tests have the disadvantage of small numbers. Miller, Kibrick, and Massell (1953) found in rheumatic subjects only a slight elevation of titres after immunization in comparison with controls. They inferred that rheumatic fever cannot be explained by hyperreactivity. Quinn, Seastone, and Dickie (1953) immunized a restricted number of rheumatic subjects and controls with pneumococcus polysaccharides and measured the antibodies by quantitative precipitation. They found no substantial difference between the two groups.

Other authors have shown the importance of incomplete antibodies in allergy (Coca and Grove, 1925; Miller and Campbell, 1947; Campbell and others, 1950; Sherman and others, 1950; Marrack, 1951; Kuhns and Pappenheimer, 1952); many regard allergy as a pre-eminent factor in the development of rheumatism (Weintraud, 1913; Klinge, 1933; Talalajew, 1933, 1936; Rössle, 1933; Albertini and Grumbach, 1933; Alpern, 1934; Aikawa, 1945).

In the present investigation the immunological reactivity of rheumatic subjects was examined by studying the levels of complete and incomplete antibodies after a single administration of non-streptococcal antigens. A group of individuals past the acute stage of rheumatism and an adequate control group were immunized with the *Brucella abortus*.

Material

In 1952-53, a large hostel for apprentices in Bohemia was affected by a streptococcal epidemic accompanied by a high incidence of rheumatic fever. In the period of a few months, scores of apprentices fell ill with this disease, and most of the patients were admitted to hospital. Those to be tested were chosen according to the data given by the hospital.

The rheumatic subjects numbered 42 (23 boys and nineteen girls) with an average age of 16 years (88·4 per cent. were just 16, four were 17 or 18, and one was 15). They had all had acute rheumatism: 24 (57·1 per cent.) not more than 1 year before, twelve (28·5 per cent.) 1 to 2 years before, and six more than 2 but less than 7 years before. Ten (23·8 per cent.) had had more than one attack of the disease.

All the rheumatic subjects were examined thoroughly for signs of persistence of sequelae of the disease. In eight (19 per cent.) conditions due to a past rheumatic endocarditis with valvular defects were found. At the time of the examination, none had an erythrocyte sedimentation rate higher than 10 mm./hr. No other symptoms of activity of the disease were present at the time of the immunization procedure.

The control group consisted of 51 apprentices of the same school, all from the same class and all 16 years old.

They were clinically examined for signs of any previous rheumatic disease and for brucellosis. This investigation was negative in all cases. None of the controls showed any symptoms of cardiac abnormality.

Before immunization, blood samples were examined for the presence of anti-brucella complete and incomplete antibodies. In all cases the result was negative. On the same day, all subjects were injected subcutaneously in the left arm with 0·5 ml. brucella bacteria. No reactions were observed either immediately or later. Blood samples for serological examination were taken on the 5th, 9th, 14th, and 19th days after immunization, and were examined within 2 days. In the course of the experiments, no rheumatic or control subjects contracted intercurrent disease, and no case of activation of rheumatism occurred.

Methods

Medium for *Brucella abortus* Culture.—500 gr. crushed bovine liver were put into 1,000 ml. water, boiled for 2 hrs on a low flame, and then filtered through paper. Water was added up to the original volume. 20 gr. peptone and 5 gr. salt were added and the solution was slightly alkalinized (7·2). Then 20 gr. washed agar weed were dissolved in the liquid, and the suspension was sterilized at 115° C. for 30 min. Non-filtered medium was put into Colle tubes, and sterilized for another 20 min. The final *p*H was usually 6·6 to 6·8.

Antigen.—A strain of *Brucella abortus** was used and inoculated into oblique agar. After a 24-hr growth at 37° C., this was washed with Ringer solution, and the suspension was transferred to the surface of the liver agar in a number of tubes. After incubation at 37° C. for 48 hrs the culture was washed with a small quantity of Ringer solution with 0·002 per cent. merthiolate. The suspension was heated to 60° C. for 30 min., diluted according to the McFarland scale No. 4, put into small vessels for blood conservation (100 ml.), and fastened with a rubber and metallic enclosure. Then samples were taken with sterile syringes and needles for testing sterility and toxicity. Sterility was tested on several liver media with thioglycolate (0·5 per cent.) under aerobic and anaerobic conditions for 5 days. Toxicity was tested on three mice inoculated intraperitoneally with 0·2 ml., 0·3 ml., and 0·5 ml. of the suspension respectively. The animals showed no symptoms of the disease for 14 days.

Serological Tests.—Serum was diluted with Ringer solution in geometric progression from 1·4 to 1·2048 in agglutination test tubes of 0·25 ml. each. To every dilution of the serum was added 2·25 ml. *Brucella abortus* suspension prepared in the same manner as for immunization but diluted according to McFarland scale No. 2. After mixing, it was incubated in a water bath at 45° C. for 18 hrs. Agglutinations were read with the naked eye against a dark background in oblique light while the test tubes were slowly rotated. The first and the last tube showing globular agglutination were recorded as the limits of the positive titre. All test tubes with a negative reaction were tested for incomplete antibodies, using the antiglobulin serum (Coombs, Mourant, and Race, 1945). The test tubes were centrifuged and the liquids poured off. Ringer solution was liberally added, and the sediment was resuspended and recentrifuged. This process was repeated four times. Finally the sediment was resuspended in 0·25 ml. serum against human globulin, diluted by Ringer solution so as to obtain in the solution twice the quantity of its final titre.

The potency of the serum was measured by collodial agglutination with human gamma globulin.† This process was also carried out with a negative serum, for purposes of control. The suspension was then incubated at 45° C. for one hour and read. The sediment was shaken.

A homogeneous suspension was recorded as a negative result. Positive agglutinations now and then showed rather small globules, and the results were therefore read with a low-power agglutinoscope.

As only the test tubes with negative reaction could be tested for incomplete antibodies, the question arose how to evaluate incomplete antibodies in the test tubes with positive reaction, *i.e.* showing globular agglutination. Here, incomplete antibodies may be present in the same quantities as normal agglutinins, or in smaller quantities, or may be missing altogether. With existing methods this cannot be ascertained. These cases were evaluated as if incomplete antibodies occurred in them up to the titre of normal antibodies. This valuation is explained below.

Results

No agglutinins were found in the sera of any investigated subject taken on the 5th day after immunization. Incomplete antibodies were found in two controls and seventeen rheumatic subjects, but in low titres only, the maximum being 1·16. On the ninth day agglutinins appeared in the sera of six controls and ten rheumatic subjects, and incomplete antibodies in fifteen controls and nineteen rheumatic subjects. The number of reacting subjects in these two tests was too small to be used for reliable statistical comparison. Therefore only the results obtained from the reactions of sera taken 14 and 19 days after immunization were compared.

The results of the examination of samples collected after 14 and 19 days appear in Table I, which shows that after 14 days nine rheumatic persons (21·4 per cent. of 42) showed no agglutinins, whilst the remaining 33 (78·6 per cent.) produced agglutinins up to titre 1·8, as well as up to titre 1·16 and even 1·32; in titre 1·64 there were not more than 28 positive cases (66·7 per cent.). To take another instance, examination for incomplete antibodies of samples taken after 19 days show eight negative cases out of fifty controls (16 per cent.) and none in the rheumatic group; in titre 1·8 there are 42 positive controls

* Furnished by the courtesy of Dr. John, Charles University, Institute of Medical Microbiology.

† For technique see Wagner (1954).

TABLE I

BASIC DATA OBTAINED IN TESTS

Numbers given in this Table serve to compute values appearing in Tables II and III, as described in the text

Blood Samples taken after		14 Days								19 Days							
Group		Control				Rheumatic				Control				Rheumatic			
		A		*IA*		*A*		*IA*		*A*		*IA*		*A*		*IA*	
		abs.	per cent.	abs.	per cent.	abs.	per cent.	abs.	per cent.	abs.	per cent.	abs.	per cent.	abs.	per cent.	abs.	per cent.
Total Cases		51		51		42		42		50		50		41		41	
Negative Cases		29	56·9	20	39·2	9	21·4	0	0·0	25	50·0	8	16·0	3	7·3	0	0·0
Positive Cases up to Titre	1 : 8	22	43·1	31	60·8	33	78·6	42	100·0	25	50·0	42	84·0	38	92·7	41	100·0
	1 : 16	22	43·1	30	58·8	33	78·6	42	100·0	25	50·0	41	82·0	38	92·7	41	100·0
	1 : 32	21	41·2	28	54·9	33	78·6	42	100·0	25	50·0	38	76·0	37	90·3	41	100·0
	1 : 64	18	35·3	26	51·0	28	66·7	42	100·0	23	46·0	33	66·0	33	80·6	40	97·6
	1 : 128	9	17·6	15	29·4	22	52·4	42	100·0	17	34·0	20	40·0	24	58·5	36	87·8
	1 : 256	4	7·8	10	19·6	14	33·3	38	90·5	8	16·0	14	28·0	13	31·7	27	65·9
	1 : 512	2	3·9	8	15·7	8	19·0	32	76·2	3	6·0	8	16·0	4	9·8	17	41·5
	1 : 1,024	1	2·0	1	2·0	0	—	19	45·2	0	—	0	—	1	2·4	7	17·1
	1 : 2,048	0	—	0	—	0	—	3	7·1	0	—	0	—	0	—	3	7·3
	1 : 4,096	0	—	0	—	0	—	1	2·4	0	—	0	—	0	—	0	—
	1 : 8,192	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—

Columns marked *A* indicate absolute numbers as well as percentages of cases reacting by normal agglutinins, or lacking these. Columns marked *IA* contain the same indications as to incomplete antibodies.

(84 per cent.) and 41 positive rheumatic subjects (100 per cent.).

Fig. 1 shows the number and percentage of all subjects reacting positively, without regard to the titre of antibodies. After 14 days, 43·1 per cent. of the controls had developed normal agglutinins, as against 78·6 per cent. in the rheumatic group (significant at the 1 per cent. level). Incomplete antibodies were found in the sera of 60·8 per cent. of the controls and in all the rheumatic subjects (significant at the 1 per cent. level). After 19 days, 50 per cent. of the controls agglutinated as against 92·7 of the rheumatic subjects (significant at the 1 per cent. level). Reaction by incomplete antibodies at this stage was 84·0 per cent. in the control group and again 100 per cent. in the rheumatic group (significant, but only at the 5 per cent. level).

Fig. 2 (overleaf) shows the percentage of subjects reacting positively to different solutions of sera. The real values arrived at are given by the graph, and the line connecting them makes a logistic curve appropriately corresponding to these values. The maximum deviations of the curves are shown by the graph. In order to establish whether the ascertained differences in the course of the curves are significant these series of percentage values were compared as follows:

Let $x_1, x_2, \ldots x_m$ and $y_1, y_2, \ldots y_n$ be the ordered results of two random samples of sizes m and n, taken from two populations with cumulative distribution functions $F_m(x)$ and $F_n(x)$.

Let $S_m(x)$ be the proportion of the m observed values x_1 less than or equal to x, and $S_n(x)$ be the proportion of the n observed values y_1 less than or equal to x.

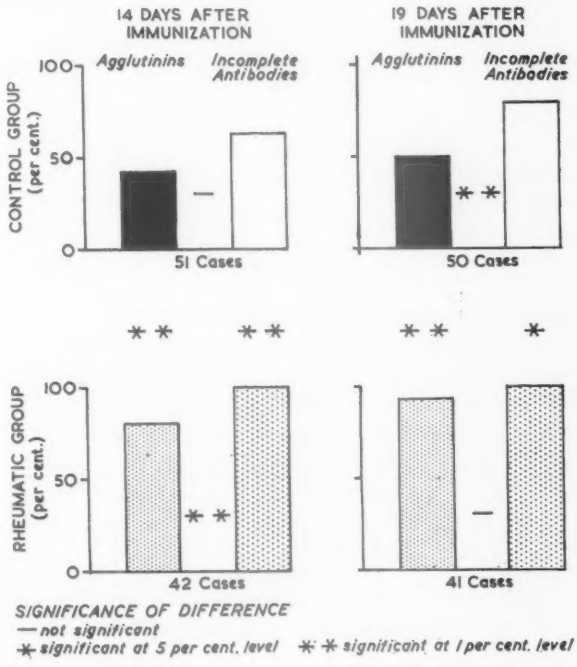

Fig. 1.—Percentage positive cases in control and rheumatic groups 14 and 19 days after immunization.

Then the expression $d = \max [S_m(x) - S_n(x)]$ can be used to test the hypothesis $F_m(x) = F(x)$, the limiting distribution $z = d\sqrt{mn/(m+n)}$ being derived and tabled. In these Tables values $P(z \geqslant z_o)$ are given, *i.e.* the probability with which we can observe values of z equal to or greater than our value z_o.

TABLE II

COMPARISON OF AGGLUTININS (*A*) AND INCOMPLETE ANTIBODIES (*IA*) 14 AND 19 DAYS AFTER IMMUNIZATION OF CONTROLS AND RHEUMATIC SUBJECTS

Valuation of maximum difference of positive percentages in comparison with:	All Cases				All Positive Cases			
Blood Samples taken after . .	14 days		19 days		14 days		19 days	
Group	Control	Rheumatic	Control	Rheumatic	Control	Rheumatic	Control	Rheumatic
m; n	51; 51	42; 42	50; 50	41; 41	22; 31	33; 42	25; 42	38; 41
d (per cent.)	17·7	57·1	34·0	34·1	16·7	52·0	−20·4	31·7
T	1 : 4 1 : 8	1 : 256 1 : 512	1 : 4 1 : 8	1 : 256	1 : 512	1 : 512	1 : 128	1 : 256
z_0	0·89	2·63	1·70	1·54	0·60	2·24	0·81	1·41
$P\ (z \geqslant z_0)$ per cent.	42·1	<0·1	0·7	1·9	87·7	<0·1	54·4	4·0

m = number of cases A $\quad$ n = number of cases IA $\quad$ $z_0 = d \cdot \sqrt{m.n/(m+n)}$
d = maximum percentual difference between number of reacting subjects in IA and A.
T = titre in which the difference d was reached.

The formula which was applied as a means for computing the values pictured by Fig. 2 has been expounded by Massey (1950), Wald and Wolfowitz (1939), Feller (1948), and other writers. It is a convenient method of estimating statistical data of this kind.

Table II shows primarily the differences between agglutinins and incomplete antibodies in the control group and in the rheumatic group as well as some contingent data. It must be read with constant reference to Table I.

The left-hand section of Table II gives the maximum differences between reacting subjects in incomplete antibodies (*IA*) and agglutinins (*A*) in percentages of all cases tested in the respective group and in the respective sample collection. This maximum difference (*d*) can be found by subtracting the percentages indicated in Table I.

E.g.: The maximum difference between *A* and *IA* in the controls after 14 days (col. 1) is in titre 1 : 4 and 1 : 8 (line 3) in which the positive cases reach 43·1 per cent. for *A* and 60·8 per cent. for *IA* respectively, as indicated in Table I. The difference between these two percentages is 17·7 per cent. (line 2). Similarly, *d* in the rheumatic group after 19 days (col. 4) is in titre 1·256 and is equal to 65·9 per cent −31·7 per cent. = 34·2 per cent., etc. (The slight discrepancy of 0·1 per cent. against the value indicated in Table II is due to the rounding off of percentages necessitated by omission of the hundredths.)

The right-hand section of Table II gives the same maximum differences, but in comparison with the positive cases only, neglecting all negative cases. These differences cannot be simply read off from Table I, as in the left-hand section, but must be computed individually.

E.g.: Col. 5 shows that the *d* in the control group after 14 days lies in the titre 1·512 and is equal to:

$$\frac{8}{31} - \frac{2}{22} = 25{\cdot}8 \text{ per cent.} - 9{\cdot}1 \text{ per cent.}$$
$$= 16{\cdot}7 \text{ per cent.}$$

In these fractions the denominators are the numbers of positive cases in each titre, and the numerators are the numbers of all positive cases in the group, collection, and type of antibody. Similarly, according to col. 8, the maximum difference in the rheumatic group after 19 days is to be found in titre 1·256 and is equal to:

$$\frac{27}{41} - \frac{13}{38} = 65{\cdot}9 \text{ per cent.} - 34{\cdot}2 \text{ per cent.}$$
$$= 31{\cdot}7 \text{ per cent.}$$

Table III (opposite) compares the control group and the rheumatic group as regards agglutinins and incomplete antibodies. The values in this Table were arrived at by a similar process to that used for Table II.

The calculated differences are represented in Figs 2 and 3 (opposite) by abscissae between corresponding curves. The degrees of significance are indicated by the number of crosses. Fig. 2 shows percentages of subjects who reacted in different titres positively by normal agglutinins as well as by incomplete antibodies 14 days after the immunization. It is apparent that the difference between normal agglutinins in both groups is significant, but only at the 5 per cent. level. There is no significant difference between agglutinins and incomplete antibodies in the control group. On the other hand, the difference between incomplete antibodies in controls and in rheumatic subjects is significant at the 1 per cent. level, the same as between the levels of incomplete antibodies and agglutinins in rheumatics. Fig. 3 shows analogous relations 19 days after the immunization. Although several differences are

TABLE III

COMPARISON OF THE CONTROL GROUP AND THE RHEUMATIC GROUP 14 AND 19 DAYS AFTER IMMUNIZATION AS REGARDS AGGLUTININS (*A*) AND INCOMPLETE ANTIBODIES (*IA*)

Valuation of maximum difference of positive percentages in comparison with:	All Cases				All Positive Cases			
Blood Samples taken after ..	14 days		19 days		14 days		19 days	
Group	A	IA	A	IA	A	IA	A	IA
m; n	51; 42	51; 42	50; 41	50; 41	22; 33	31; 42	25; 38	42; 41
d (per cent.)	37·4	70·9	42·7	47·8	25·8	58·2	−5·2	40·2
T	1 : 32	1 : 256	1 : 4 1 : 8 1 : 16	1 : 128	1 : 128	1 : 256	1 : 64	1 : 128
z_0	1·80	3·40	2·03	2·27	0·94	2·47	0·20	1·83
$P(z \geqslant z_0)$ per cent.	0·3	<0·1	0·1	<0·1	35·3	<0·1	>99·9	0·3

m = number of cases in Control group n = number of cases in Rheumatic group $z_0 = d \cdot \sqrt{m.n/(m+n)}$
d = maximum percentual difference between number of reacting subjects in Controls and Rheumatics.
T = titre in which difference d was reached.

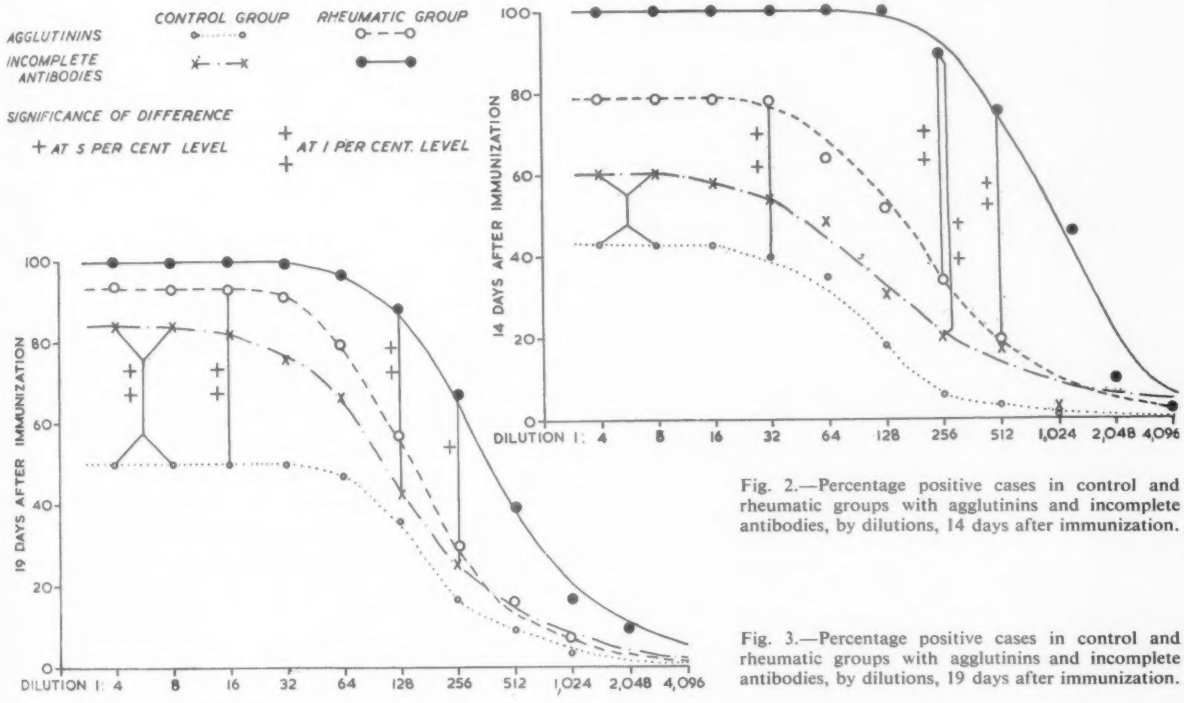

Fig. 2.—Percentage positive cases in control and rheumatic groups with agglutinins and incomplete antibodies, by dilutions, 14 days after immunization.

Fig. 3.—Percentage positive cases in control and rheumatic groups with agglutinins and incomplete antibodies, by dilutions, 19 days after immunization.

less significant as compared with Fig. 2, the significance between the curves of incomplete antibodies in both groups remains at the 1 per cent. level. The maximum difference between the numbers of reacting subjects in both groups is in titre 1·256 in both sample collections.

Figs 4 and 5 (overleaf) show the number of subjects who reacted by incomplete antibodies only up to the given titre, *i.e.* who were not positive above the level of the given titre after 14 and 19 days. It appears that after 14 days only four members of the rheumatic group reacted with a titre under 1·256. In the control group the first maximum of frequencies is in titre 1·64; the number of subjects reacting with higher titres then falls off, but it attains another maximum in titre 1·512. After 19 days the situation is analogous, but here both groups are already overlapping so that the differences between them

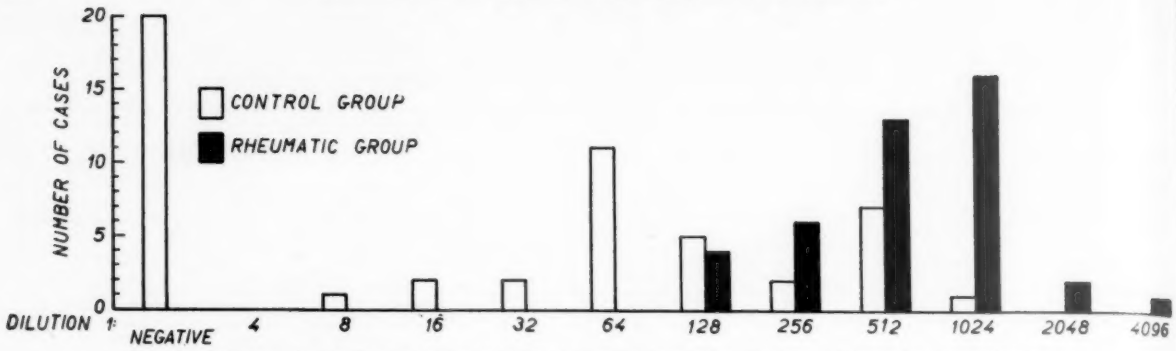

Fig. 4.—Number of positive cases in control and rheumatic groups, by dilutions, 14 days after immunization.

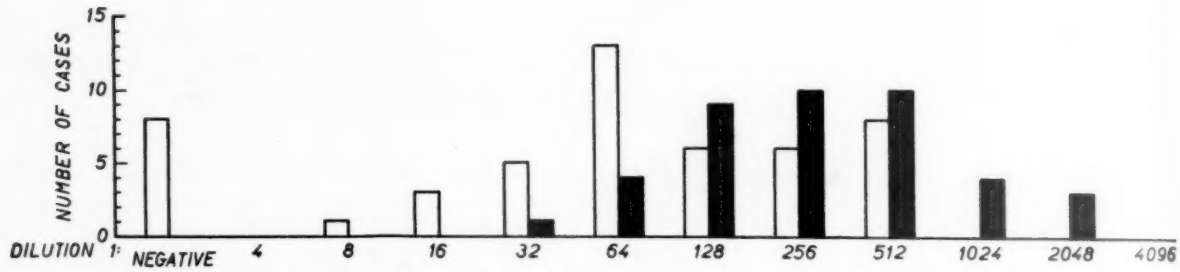

Fig. 5.—Number of positive cases in control and rheumatic groups, by dilutions, 19 days after immunization.

are not so significant. Nevertheless, it appears even here that the number of reacting subjects in the control group, after a certain decline in titre 1·128, surprisingly holds the same level in further dilutions, and only then begins to fall again.

There were ten controls and no rheumatic patients in whom, after 14 days, no higher titre was found by the antiglobulin serum than by agglutination. At this stage, there were eighteen controls and no rheumatic subjects in whom neither agglutinins nor incomplete antibodies were detected.

After 19 days, there were 21 controls and only six rheumatic patients in whom no higher titre was ascertained by means of the antiglobulin serum than by agglutination. At this stage, there were six controls and only one rheumatic patient who did not react at all, either by agglutination or by incomplete antibodies.

Discussion

The subjects investigated were very appropriate material for immunological tests. All were of the same age, lived in the same environment, and had the same food. The whole population was exposed to a fortuitous infection as a result of which a number contracted rheumatic fever. We may therefore consider the observed differences in the immunological responses to be real differences in the reactivity of the subjects. We do not feel entitled to decide whether these differences are due to heredity or to the influence of external conditions which were active before joining the said population. At any rate, we may call them the immunological constitution of the investigated subjects.

From the methodological approach, the use of brucella bacteria appeared advantageous. Suspensions of this bacteria permit not only the investigation of agglutination antibodies, but particularly the convenient investigation of incomplete antibodies which are to be found regularly in natural contagions by this microbe (Griffitts, 1947; Renoux, 1950; Carrère and Renoux, 1951; D'Alessandro and Celano, 1950; Hall and Manion, 1953). Another reason for utilizing brucella was that antibodies do not usually occur in normal population in this age and vocational group. A further advantage was that this antigen did not provoke untoward reactions in the quantities used.

The results obtained after 5 and 10 days already showed convincingly that rheumatic subjects develop antibodies more readily, especially those of the incomplete type. Nevertheless, these results could not be made use of for statistical conclusions in default of sufficiently high numbers.

The differences found after 14 days between the two groups did not appear quantitatively great when measured by normal agglutination reactions, but were statistically significant. The exactitude of the ascertained relations is warranted by the relatively

large number of investigated subjects. Creger and others (1951), though their results agree with ours, were not able to support their contention by convincing statistics. Nor could Miller and others (1953) or Quinn and others (1953) establish statistical significance of the difference between rheumatics and controls by means of normal antibodies.

On the other hand, the quantitative aspects of the development of incomplete antibodies differ fundamentally from those of normal antibodies. The difference in the levels shown in the graphs is statistically highly significant. Certain rheumatic subjects develop antibodies after as little as 8 days, and after 14 days 100 per cent. of them are positive as against 60 per cent. of the controls. Since no rheumatic subject was negative, it was possible to average the titre at 1·792, with no value under 1·128. 40 per cent. of the controls were negative. Statistical considerations, allowing only positive cases to be used for determining the average titre and omitting the negative cases, lead to a certain distortion of the picture; nevertheless, the average titre was between 1·64 and 1·128. The incidence of different titres in the control group (Figs 4 and 5) shows a greater dispersion of frequencies than that of the rheumatic group. The controls show a further and unexpected rise of incidence in the titres around 1·512. Further observations are necessary to determine whether these controls are in fact potential rheumatics, so far spared on unknown grounds, or allergics in whom a hitherto unproved analogous immunological reactivity may be assumed.

The control group included a certain number of subjects in whom incomplete antibodies could not be revealed by the method employed, as their titre did not exceed that of normal agglutinins. We have based our calculations on the surmise that incomplete antibodies were present in these subjects in the same titre as normal agglutinins. In other words, we have chosen the least favourable alternative for the demonstration of the increased development of incomplete antibodies in rheumatics in comparison with normal subjects.

On the strength of general immunological experience the antigen dosage may be assumed to influence the development of antibodies. In our tests we have chosen the dose nearly at random by applying McFarland's scale 4 as the standard of turbidity. On the basis of several preliminary tests we concluded that this quantity would lead to the formation of an exactly measurable amount of antibodies. Although the results are significant, it may be that the dose applied was too large, since a single injection produced antibodies in 80 per cent. of controls. Further tests will determine whether the difference between the two groups will increase with a lowering of the antigen dosage.

It is necessary to examine the exact role of an increased ability to develop antibodies in the pathogenesis of rheumatism. A number of communications show that incomplete antibodies are an important factor in the origin of allergic diseases (Coca and Grove, 1925; Miller and Campbell, 1947; Campbell and others, 1950; Sherman and others, 1950; Manack, 1951; Kuhns and Pappenheimer, 1952). Allergy has for a long time been suspected of partaking in the development of rheumatism. The present observations give further support to the hypothesis of the allergic origin of rheumatism, but it will be necessary to direct further research to trace the incomplete antibodies to streptococcus and tissue antigens which may develop naturally in rheumatic subjects. The question of the nature and the regulating mechanism of this altered reactivity of the host remains open.

Summary

A group of 42 convalescents from rheumatic fever and 51 healthy subjects were given a single inoculation of *Brucella abortus* bacteria in one dose. Titres of normal agglutinins and of incomplete antibodies were ascertained from blood samples taken after 5, 8, 14, and 19 days. The rheumatic subjects developed antibodies a little faster than normal persons. A small but statistically significant difference in the titres of normal agglutinins was found between the two groups, and a substantial difference appeared in the levels of incomplete antibodies. The inferences to be drawn from these quantitative and qualitative differences in reactivity are discussed, with reference to the pathogenesis of rheumatic fever.

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Les agglutinines et les anticorps incomplets après une seule inoculation d'antigène chez des sujets normaux et rhumatisants

RÉSUMÉ

On a inoculé une seule dose de bacilles *Brucella abortus* à 42 convalescents de la maladie de Bouillaud et à 51 sujets normaux. On a determiné les titres des agglutinines normales et des anticorps incomplets dans le sang pris au bout de 5, 8, 14 et 19 jours. Les rhumatisants produisaient des anticorps un peu plus vite que les sujets normaux. On trouva une différence, petite mais statistiquement significative, dans les titres des agglutinines normales entre les deux groupes et une différence appréciable dans les taux des anticorps incomplets. On discute la portée de ces différences quantitatives et qualitatives de réactivité à propos de la pathogénie de la maladie de Bouillaud.

Las aglutininas y los anticuerpos incompletos después de una sola inoculación de antígeno en sujetos normales y reumáticos

SUMARIO

Se inoculó una sola dosis de bácilos *Brucella abortus* a 42 convalecientes de reumatismo poliarticular agudo y a 51 sujetos sanos. Se determinaron los valores de aglutininas normales y de anticuerpos incompletos en la sangre recogida al cabo de 5, 8, 14 y 19 días. Los reumáticos produjeron anticuerpos algo más rapidamente que los sujetos sanos. Se observó una diferencia, pequeña pero estadisticamente significativa, en los valores de las aglutininas normales entre los dos grupos y una diferencia apreciable en las cifras de los anticuerpos incompletos. Se discuten las implicaciones de estas diferencias cuantitativas y cualitativas de reactividad en relación con la patogenesis del reumatismo poliarticular agudo.

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METACORTANDRACIN AND 9-ALPHA-FLUORO HYDROCORTISONE ACETATE IN RHEUMATIC DISEASES

BY

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Among the pharmacological problems raised by the study of the biological properties of cortisone is the existence of other substances exhibiting the same or similar properties.

Hydrocortisone is already in practical use, and although not much more active than cortisone, in the acetate form it presents greater local antiphlogistic activity. Aldosterone which has been introduced into medical use in the last 2 years, has a marked action on electrolyte metabolism, but its antiphlogistic action is nil. Recently three new steroids possessing anti-inflammatory properties superior to those of cortisone have been reported: 9-α-fluoro hydrocortisone (Boland and Headley, 1954; Ward and others, 1954), metacortandralone and metacortandracin (Bunim and others, 1955; Ballabio and others, 1955, a, b; Sala and others, 1955, a, b).

Bunim states that metacortandralone represents a great step forward in the treatment of rheumatic diseases with adrenal hormones because it is three or four times more active than cortisone, and does not affect the electrolyte and the nitrogen metabolism unfavourably, at least within the limits of therapeutically active doses.

This report deals with our clinical experience in the last 3 months in the treatment of rheumatic diseases with metacortandracin and 9-α-fluoro hydrocortisone.

Material

This study was conducted with 36 patients, some of whom have been under our control for several years. This facilitated comparison with previous treatments, as the results could be exactly defined over a long period.

Methods

Both steroids were administered orally; the total daily dosage was divided into three or four doses, according to quantity.

Initial "suppressive" doses were gradually reduced to the minimum maintenance dose. The initial dose was approximately 30-50 mg. for metacortandracin and 8-16 mg. for 9-α-fluoro hydrocortisone. The maintenance doses varied widely from case to case, ranging from 15 to 30 mg./24 hrs for metacortandracin, and from 6 to 8 mg. for 9-α-fluoro hydrocortisone. The duration of treatment was determined by the clinical course; in some cases treatment is still being continued and follows the schemes of long-term treatment already devised for cortisone. The laboratory tests used were as set out in Table I.

TABLE I
LABORATORY TESTS

Investigation	Method	
	Authors	Date
Antistreptolysin titre	Rantz and Randall	1945
Serum mucoproteins	Winzler	1948
Plasma and urinary sodium and potassium (by flame photometry)	Mosher and others	1949
Plasma chloride	Van Slyke and Hiller	1947
Urinary chloride	Harvey	1910
Serum carbon dioxide	Van Slyke and Cullen	1915
Plasma and urinary endogenous creatinine	Bonsnes and Taussky	1945
Total body fluids	Soberman	1950
Extracellular fluids	Cachera and Lamotte	1923
Blood glucose	Hagedorn and Jensen	1923
Serum albumin and globulins (by optical electrophoresis)	Tiselius	
Total serum proteins	Phillips and Van Slyke	1943
Total plasma cholesterol	Bloor	1916
Plasma uric acid	Brown	1945
Urinary uric acid	Benedict and Franke	1952
Circulating eosinophils	Dunger*	1910
Urinary 17-ketosteroids	Callow and others	1938

* Modified by Forsham and others, 1948.

Results

Anti-Rheumatic Activity.—In all cases, a marked anti-rheumatic action followed the administration of metacortandracin and 9-α-fluoro hydrocortisone. All the patients showed a marked subjective improvement within a few days, with reduction of pain and stiffness and relief of aching on motion.

The objective improvement included disappearance or reduction of muscular and articular stiffness and swelling, and lessening of articular tenderness. The consequent improvement of articular function was clearly evident, so that in many cases there was a return of activity even greater than that obtained with previous cortisone treatment. The response

PATIENTS RECEIVING CORTISONE, HYDROCORTISONE, 9-α-FLUORO HYDRO… METAC…

Case No.	Sex	Age	Diagnosis	Stage	Duration of Arthritis (yrs)	Drug	…r Hydro… …nance Do…
1	F	70	Rheumatoid arthritis	IV	20	{Cortisone {Hydrocor…	75–100 70–80
2	M	71		III-IV	8	{Cortisone {Hydrocor…	70–75 60–62
3	F	30		II-III	3	{Cortisone {Hydrocor…	100 80
4	F	59		III-IV	5	{Cortisone {Hydrocor…	70–75 50
5	M	48		II	1	{Cortisone {Hydrocor…	100 80
6	M	34		II	3	Cortisone	60–70
7	M	54		II-III	2	Cortisone	100
8	F	65		II	3	Cortisone	70–75
9	F	58		III-IV	10	Cortisone	75–100
10	F	49		II	4	Cortisone	70–75
11	F	51		III-IV	6	Cortisone	100
12	F	51		II	5	Cortisone	75
13	M	58		II-III	6	{Cortisone {Hydrocor…	70–80 60–60
14	M	63	Psoriatic arthritis	II-III	4	Cortisone	75
15	M	40		III-IV	4	Cortisone	75–100
16	M	27	Still-Chauffard disease	I-II	2	Cortisone	75
17	F	9		II-III	3	Cortisone	50
18	F	21	Rheumatic fever	Acute phase	—	—	—
19	F	69		Acute phase	—	—	—
20	M	7	Rheumatic carditis	Active	1	—	—
21	F	36		Active	4	—	—
22	F	44		Active	1	—	—
23	M	19		Active	1	—	—
24	F	17		Active	3	—	—
25	M	13	Rheumatic pancarditis	Acute phase	½	—	—
26	M	31	Viscerocarditis	Acute phase	½	Cortisone	100
27	F	23	Lupus erythematosus	Subacute phase	1	{Cortisone {Hydrocor…	50 40
28	F	64	Chronic gout	III-IV	10	Cortisone	75–100
29	M	50		II	1	—	—
30	M	60		II-III	5	Cortisone	75
31	M	35		II	5	—	—
32	F	51	Spondylo-arthritis	I	4	—	—
33	F	52	Osteo-arthritis	II	3	—	—
34	F	66		II	5	—	—
35	M	57	Scleroderma	Severe	1	Cortisone	100
36	F	57		Moderate	10	Cortisone	37·5

was rapid during the very first days of treatment and then became gradual; pain soon disappeared, but days or weeks were required to achieve the maximum effect on stiffness and swelling.

In most cases the local improvement was accompanied by disappearance of fever, haemopoietic stimulation, return of strength and appetite, increase of weight, and proportional euphoric state. This was similar to what has already been observed with Compounds E and F, so that metacortandracin and 9-α-fluoro hydrocortisone may be said to possess all the anti-inflammatory and anti-rheumatic properties of cortisone and hydrocortisone.

The case-list contained in Table II shows that the indications for metacortandracin are the same as for cortisone.

A sharp decrease was observed in the sedimentation rate (Katz index), in some cases greater than that obtained with cortisone. A decrease was observed in serum mucoproteins similar to that obtained with cortisone. The antistreptolysin titre decreased and in some cases reached values below those obtained with cortisone.

The electrophoretic pattern in some cases was clearly modified but did not become completely normal: the most important changes were represented by albumin increase and a decrease of total globulins, especially of the fraction.

Treatment with cortisone, hydrocortisone, or both, had previously been given to 23 of the 36 patients studied.

In Table II the results obtained with previous

METACORTANDRACIN AND COMPARISON OF ANTI-RHEUMATIC PROPERTIES

r Hydrocortisone Therapy			Metacortandracin and 9-α-fluoro hydrocortisone Therapy		
Drug	nance Dose	Results	Drug	Maintenance Dose	Results
{Cortisone	75–100	Moderate	Metacortandracin	20–25	Moderate
{Hydrocort	50–80	Moderate			
{Cortisone	50–75	Moderate	Metacortandracin	20	Marked
{Hydrocort	50–62	Moderate			
{Cortisone	100	Moderate	Metacortandracin	25–30	Marked
{Hydrocort	80	Moderate			
{Cortisone	50–75	Moderate	Metacortandracin	15–20	Moderate
{Hydrocort	50	Moderate			
{Cortisone	100	Moderate	{Metacortandracin	35–40	Marked}
{Hydrocort	80	Moderate	{9-α-fluoro hydrocortisone	8–10	Marked}
Cortisone	50–70	Moderate	9-α-fluoro hydrocortisone	8	Marked
Cortisone	100	Moderate	Metacortandracin	25	Marked
Cortisone	50–75	Moderate	Metacortandracin	15–20	Marked
Cortisone	75–100	Moderate	Metacortandracin	20	Marked
Cortisone	50–75	Marked	Metacortandracin	20	Marked
Cortisone	100	Marked	Metacortandracin	25	Marked
Cortisone	75	Moderate	Metacortandracin	25–20	Marked
{Cortisone	70–80	Marked	Metacortandracin	25–20	Marked
{Hydrocorti	50–60	Marked			
Cortisone	75	Marked	Metacortandracin	20	Very marked
Cortisone	75–100	Moderate	Metacortandracin	30	Moderate
Cortisone	75	Moderate	Metacortandracin	15	Very marked
Cortisone	50	Marked	Metacortandracin	15	Marked
—	—	—	Metacortandracin	25	Very marked
—	—	—	Metacortandracin	25	Very marked
—	—	—	Metacortandracin	20	Marked
—	—	—	Metacortandracin	25	Marked
—	—	—	Metacortandracin	20	Marked
—	—	—	Metacortandracin	20	Marked
—	—	—	Metacortandracin	20	Marked
—	—	—	Metacortandracin	25	Marked
Cortisone	100	Marked	Metacortandracin	30	Very marked
Cortisone	50	Marked	{Metacortandracin	15	Very marked
Hydrocort	40	Very marked	{9-α-fluoro hydrocortisone	8	Very marked
Cortisone	75–100	Moderate	Metacortandracin	25	Moderate
—	—	—	Metacortandracin	20	Very marked
Cortisone	75	Marked	Metacortandracin	20	Marked
—	—	—	{9-α-fluoro hydrocortisone	4·8	Very marked
			{Metacortandracin	15	Very marked
—	—	—	Metacortandracin	25	Moderate
—	—	—	Metacortandracin	20	Marked
—	—	—	Metacortandracin	25	Marked
Cortisone	100	Moderate	Metacortandracin	20	Moderate
Cortisone	37·5	Moderate	Metacortandracin	20	Marked

cortisone and hydrocortisone treatments are compared with those obtained with metacortandracin therapy: the new steroid, in maintenance doses three to four times less than those required with cortisone, produces a greater effect.

Side-Effects.—Table III summarizes the secondary effects which were observed, those seen with cortisone treatment being used as a reference.

All the side-effects were transient and ceased when treatment was withdrawn.

Of all the data given in Table III the most important are those presumably related to increased corticoid activity.

TABLE III

OCCURRENCE OF SIDE-EFFECTS

Side-effects	9-α-fluoro hydrocortisone	Meta-cortandracin
Oedema	+ + +	− − −
Increase of blood pressure ..	+ + −	− − −
Increased appetite	+ − −	+ + −
Epigastric discomfort	− − −	+ − −
Hirsutism	− − −	+ − −
Facial rounding	+ + −	+ + −
Mental changes	+ − −	+ − −
Increased sweating	+ − −	+ − −
Acne	− − −	+ − −
Erythema	− − −	± − −
Sleeplessness and restlessness ..	+ − −	+ + −

Fluid Balance.—Oedema and oliguria never occurred during treatment with metacortandracin, but they were very evident during treatment with 9-α-fluoro hydro-

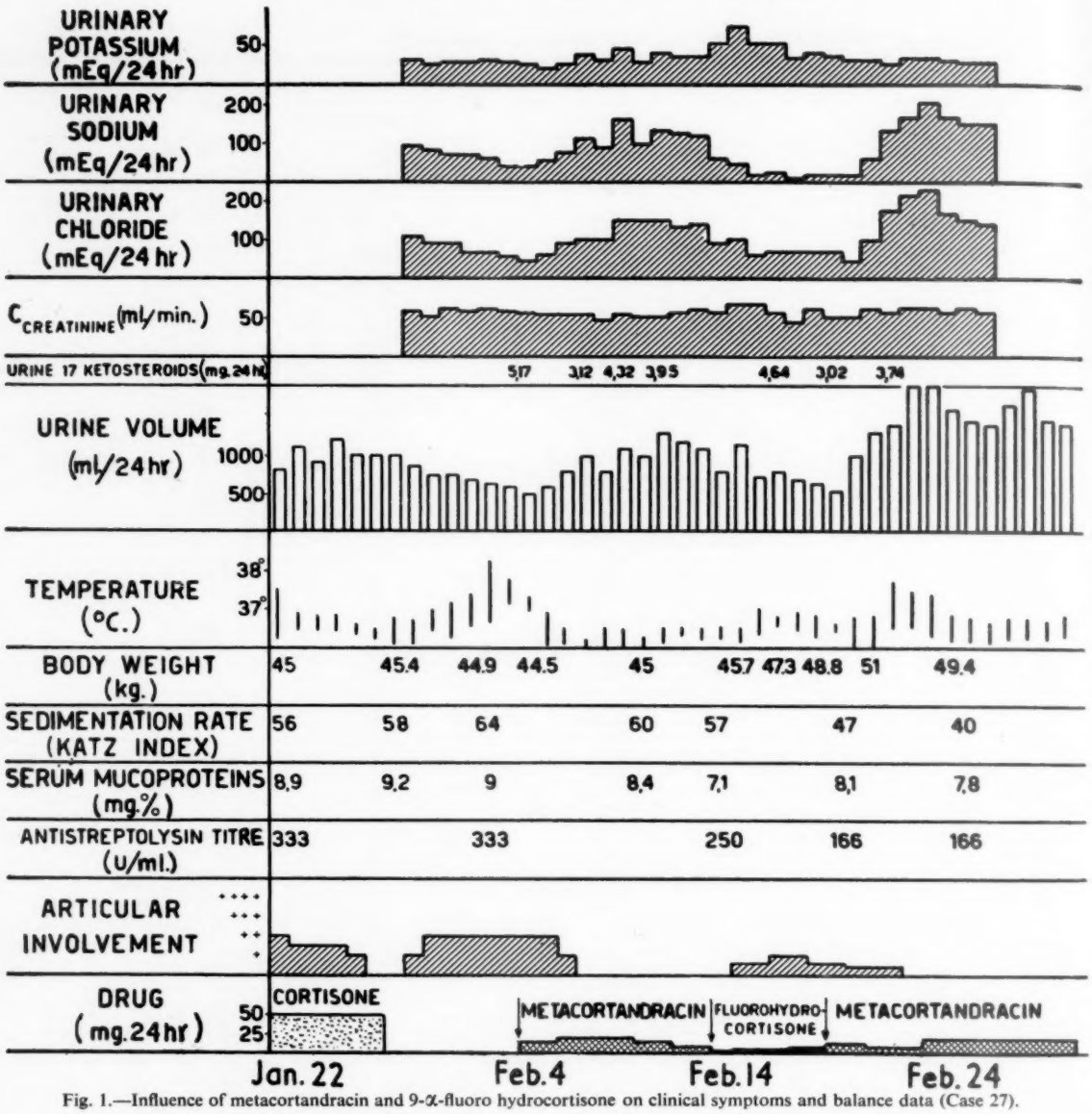

Fig. 1.—Influence of metacortandracin and 9-α-fluoro hydrocortisone on clinical symptoms and balance data (Case 27).

cortisone, when there were often rapid gains in weight (Figs 1 and 2, Cases 27 and 5).

Blood Pressure.—This is not modified by metacortandracin, but is constantly increased by 9-α-fluoro hydrocortisone (20-40 mm. Hg).

Hypercorticoidism.—Rounding of face, acne, and hirsutism varied in relation to the dosage, length of treatment, and patient's physique.

Psychiatric Effects.—Clinical features characteristic of mania was observed in one case treated with metacortandracin and one case treated with 9-α-fluoro hydrocortisone.

Progress after Suspension of Treatment.—Relapses occurred on discontinuing treatment in the cases observed up to the present.

The symptoms returned within a few days, causing a rebound relapse, already described by Hench in cortisone administration.

We never observed patterns of true deterioration of the type defined as "withdrawal syndrome", but the periods of administration are still too short for a final opinion to be expressed.

Metabolic Effects

Salt and Water Balance.—There was a marked difference between the effect of 9-α-fluoro hydro-

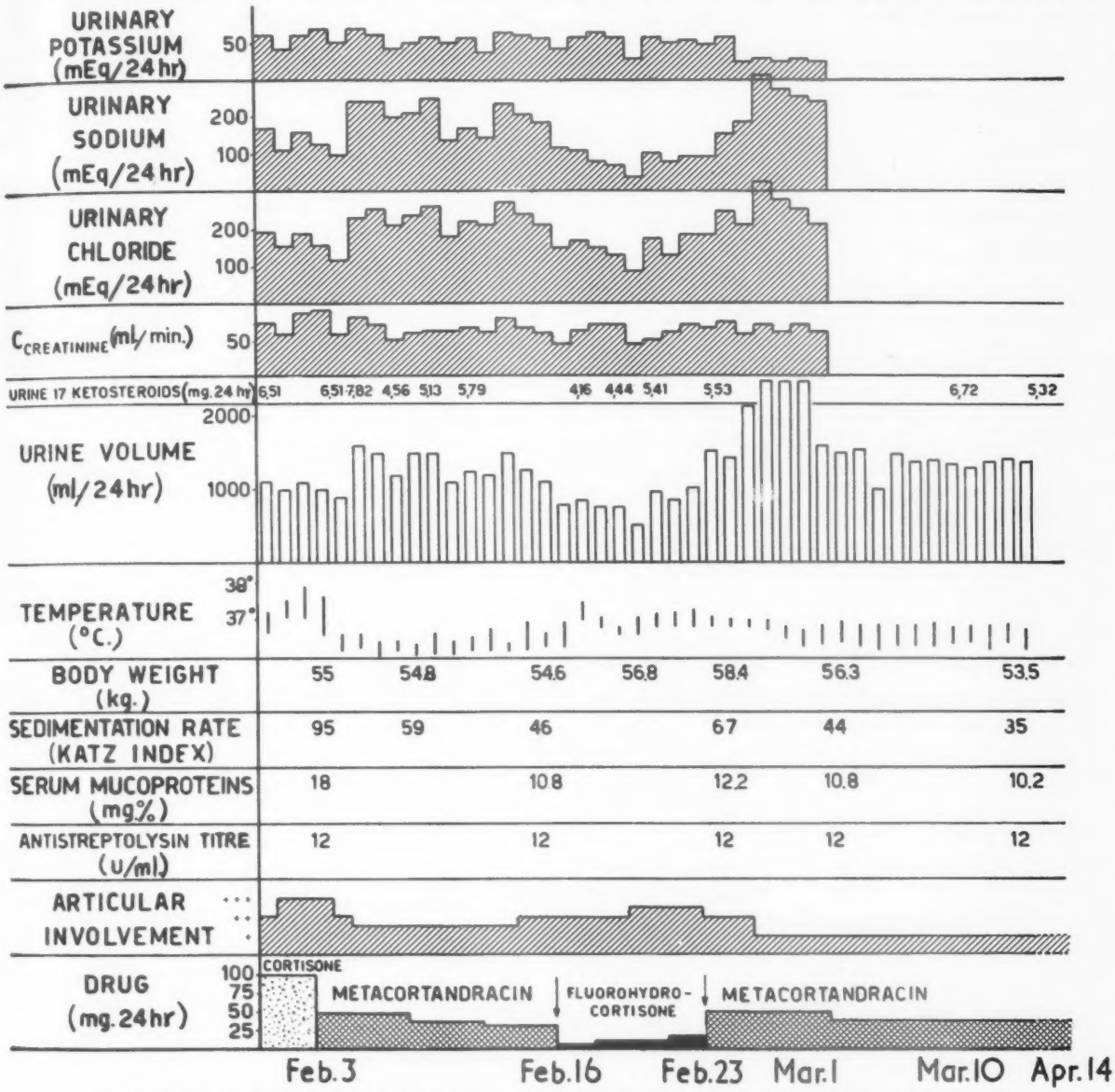

Fig. 2.—Influence of metacortandracin and 9-α-fluoro hydrocortisone on clinical symptoms and balance data (Case 5).

cortisone and metacortandracin. The former caused oliguria with retention of Na and Cl, rapid increase in body weight, and sometimes loss of K (Figs 1 and 2). The constancy of the endogenous creatinine clearance makes the sodium and chloride retention referable to tubular reabsorption.

Metacortandracin does not produce a positive sodium balance; it is evident from our cases that it has a diuretic effect and increases the elimination of sodium and chloride; the increased output of sodium into the urine may be explained by inhibition of tubular reabsorption (Figs 1 and 2).

Metacortandracin does not markedly modify the concentration of plasma electrolytes, 9-α-fluoro hydrocortisone increases plasma sodium and chloride and markedly reduces plasma potassium, to the point of reaching pathological values (Fig. 3, overleaf), with possible alterations of the electrocardiogram by lengthening of Q-T space and displacing the S-T segment, depression of T wave, appearance of U wave. In every case, a fall of haematocrit occurred, as an expression of hydraemia and haemodilution.

Both extracellular and intracellular water increased under 9-α-fluoro hydrocortisone, while metacortandracin did not modify the fluids compartments.

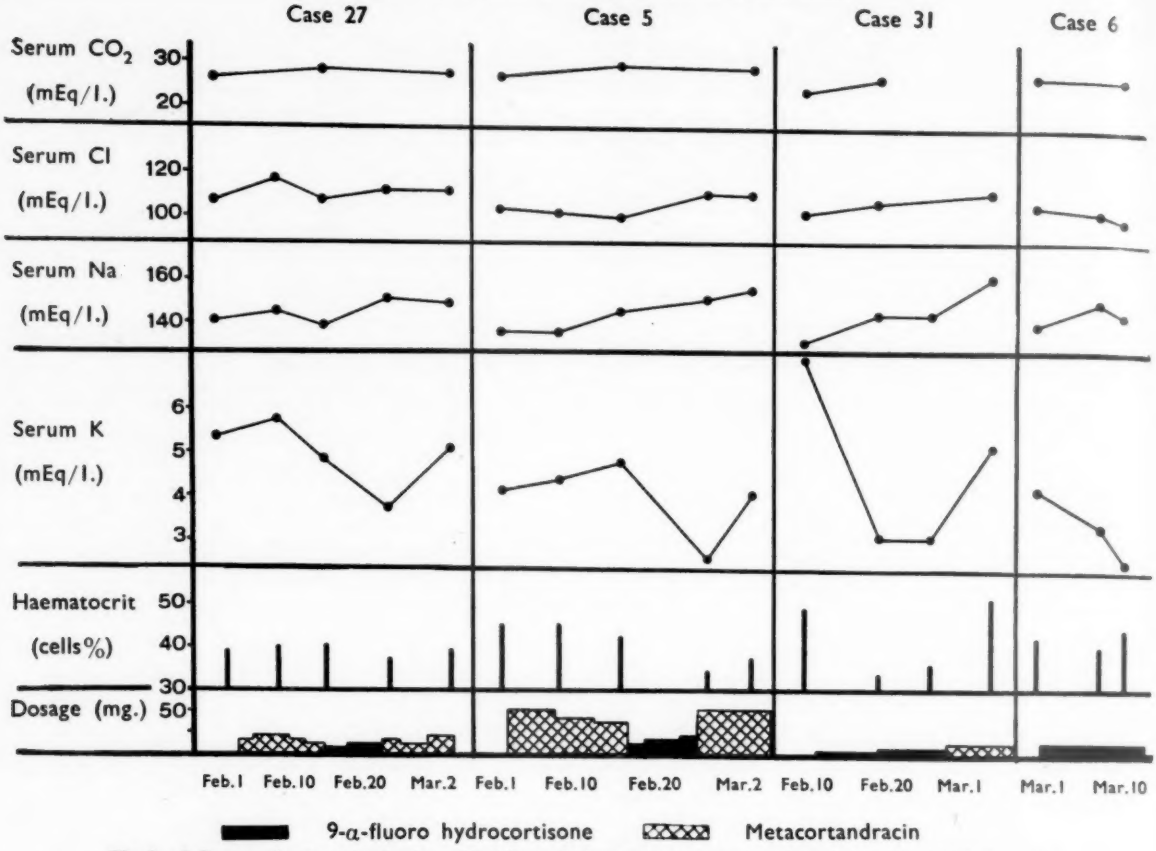

Fig. 3.—Influence of metacortandracin and 9-α-fluoro hydrocortisone on serum electrolytes in four typical cases.

Carbohydrate Metabolism.—In four subjects with normal carbohydrate metabolism we determined the effect of both hormones on the glucose tolerance (glucose total load of 0·75 g./kg.) and on the sensitivity to insulin (Himmsworth's test: per cent. variations in blood glucose after injection of 30 g./m.^{2} glucose and intravenous injection of 5 U/m.^{2} insulin). Both hormones reduced the sensitivity to insulin, and in three cases metacortandracin reduced the glucose tolerance.

We have observed the appearance of glycosuria in one of these cases, and also in another case of acute leukaemia treated with 75 mg. metacortandracin daily. In one case with diabetes, metacortandracin caused definite increase of urinary and blood sugar.

Serum Proteins and Cholesterol.—Metacortandracin tended to normalize the serum protein errors present in rheumatoid arthritis, causing increased albumin and reduction in globulins. 9-α-fluoro hydrocortisone was less effective probably owing to the shorter duration of treatment.

On serum cholesterol, 9-α-fluoro hydrocortisone appears to have no action, but metacortandracin sometimes increased the total serum cholesterol.

Uric Acid.—The effects on uric acid metabolism was studied in two normal and four gouty subjects. In normal subjects 9-α-fluoro hydrocortisone and metacortandracin caused no change in blood uric acid levels; the urinary uric acid seems to fluctuate more with urine volume than with the administration of hormones.

Four cases of gout were treated with metacortandracin: there was a favourable effect on the symptomatology, a slight reduction in blood uric acid, and a slight increase in the daily urinary output of urates. The increased excretion of urates may be attributed to the inhibition of tubular reabsorption of urates.

Adrenal Function.—Metacortandracin significantly and constantly lowered the level of blood eosinophils, while 9-α-fluoro hydrocortisone had no such action (Figs 1 and 2).

The levels of urinary 17-ketosteroids were decreased by hormonal administration even in those cases whose excretion was abnormally low, owing to former cortisone therapy.

Comment

Metacortandracin was found to have three to five times more anti-rheumatic activity and 9-α-fluoro hydrocortisone eight to ten times more than cortisone.

9-α-fluoro hydrocortisone exerts a strong mineralocorticoid activity which leads to water and sodium retention and potassium excretion, and to an increase of body fluids in both extracellular and intracellular space; the decrease in plasma potassium was especially marked. These effects explain the increase in body weight and blood volume, the appearance of oliguria and oedema, the increase in blood pressure, bradycardia, and some E.C.G. changes.

On the other hand, metacortandracin does not interfere unfavourably with water and salt balance, and may even increase sodium and water excretion. This absence of water and sodium retention is sufficient for us to consider metacortandracin useful in anti-rheumatic therapy, not only in avoiding secondary phenomena but also in enabling anti-rheumatic therapy to be extended to cases which were previously considered hazardous, particularly those with active carditis complicated by heart failure.

Both steroids produce a state of hypercorticoidism (acne, hirsutism, rounding of face, etc.) and inhibit adrenal function, as evidenced by the decrease of urinary 17-ketosteroids. The extent of this action will be tested by long-term schedules of treatment.

Biological Considerations.—In metacortandracin the potentiation of the anti-rheumatic and anti-phlogistic properties is combined with the loss of one of the most important metabolic actions of corticoid hormones. The possibility of a dissociation between metabolic and anti-phlogistic properties is suggested, and this observation should lead to a further search for steroids with exclusive or predominant anti-inflammatory activity.

The fact that 9-α-fluoro hydrocortisone is a stronger mineralocorticoid than desoxycorticosterone and also possesses anti-inflammatory properties seems to minimize the possibility of the existence of two groups of opposite corticoids, the former having mineralo-active and prophlogistic properties and the latter glyco-active and anti-phlogistic properties.

Summary

(1) The anti-rheumatic activity of metacortandracin and 9-α-fluoro hydrocortisone is 3 to 5 and 8 to 10 times stronger than cortisone.

(2) Metacortandracin does not interfere with salt and water balance; glucose tolerance and insulin sensitivity are decreased; pre-existing diabetes is aggravated.

(3) The absence of mineral activity in metacortandracin represents a step forward in anti-reactional therapy and allows the extension of anti-rheumatic therapy to forms of active carditis complicated by heart failure.

(4) 9-α-fluoro hydrocortisone has a marked mineralocorticoid activity; it increases sodium re-absorption and potassium excretion, and increases both extracellular and intracellular fluids. The serum potassium levels are much reduced, Na values very slightly increased, and haematocrit values reduced.

(5) The increased effect of 9-α-fluoro hydrocortisone on electrolytes lessens its usefulness in the treatment of rheumatic diseases.

(6) Both steroids produce a state of hypercorticoidism and inhibit adrenal function; metacortandracin decreases the circulating eosinophils.

(7) Since the anti-rheumatic activity of 9-α-fluoro hydrocortisone was demonstrated, no relationship between the mineral and prophlogistic activity of the corticoids has been apparent.

The metacortandracin was kindly supplied by Lepetit S.A., and the 9-α-fluoro hydrocortisone by Farmitalia S.A.

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La métacortandracine et l'acétate de 9-α-fluoro hydrocortisone dans les malades rhumatismales

RÉSUMÉ

(1) L'action antirhumatismale de la métacortandracine et de la 9-α-fluoro hydrocortisone est 3 à 5 et 8 à 10 fois plus forte que celle de la cortisone.

(2) La métacortandracine ne dérange pas l'équilibre salin et aqueux; diminue la tolérance du glucose et la sensibilité à l'insuline; aggrave le diabète préexistant.

(3) Le fait que la métacortandracine n'agit pas sur les minéraux est un grand pas dans la thérapie anti-réactionnelle et permet d'appliquer le traitement anti-rhumatismal aux formes de cardite active compliquée d'insuffisance cardiaque.

(4) La 9-α-fluoro hydrocortisone a une action minéralocorticoide marquée: elle augmente la re-absorption du sodium, l'excrétion du potassium et la rétention liquide intra et extracellulaire. Le taux sérique du potassium est très réduit, celui du sodium un peu augmenté et le chiffre obtenu au moyen de l'hématocrite est diminué.

(5) La plus forte action de la 9-α-fluoro hydrocortisone sur les électrolytes la rend moins utile dans le traitement des maladies rhumatismales.

(6) Les deux stéroïdes produisent un état d'hyper-corticoidisme et inhibent la fonction surrénale; la méta-cortandrine diminue le chiffre sanguin des éosinophiles.

(7) A la suite de la découverte de l'action anti-rhumatismale de la 9-α-fluoro hydrocortisone, on n'a observé aucun rapport entre l'action des corticoïdes sur les minéraux et sur l'inflammation.

La metacortandracina y el acetato de 9-α-fluoro hidrocortisona en las enfermedades reumáticas

SUMARIO

(1) La acción antirreumática de la metacortandracina y de la 9-α-fluoro hidrocortisona es 3 a 5 y 8 a 10 veces más fuerte que la de la cortisona.

(2) La metacortandracina no estorba el equilibrio salino o acuoso; disminuye la tolerancia de la glucosa y la sensibilidad a la insulina; agrava la diabetes existente.

(3) El hecho de que la metacortandracina no tiene acción mineral constituye un adelanto de la terapia antirreaccional, ya que facilita el tratamiento antir-reumático de las formas de carditis activa con insuficiencia cardiaca.

(4) La 9-α-fluoro hidrocortisona tiene una acción mineralocorticoide marcada: aumenta la reabsorpción de sodio, la excreción de potasio y la retención líquida intra y extracelular. Las cifras séricas de potasio se ven reducidas, las de sodio algo aumentadas y los valores de hematocrito disminuidos.

(5) Por su acción más fuerte sobre electrolitos, la 9-α-fluoro hidrocortisona es menos util en el tratamiento de las enfermedades reumáticas.

(6) Ambos esteroides producen un estado de hiper-corticoidismo e inhiben la función suprarrenal; la meta-cortandracina hace bajar las cifras sanguíneas de eosinófilos.

(7) La descubierta de la acción antirreumática de la 9-α-fluoro hidrocortisona no reveló relación alguna entre la acción mineral y antiflogística de los corticoides.

ADDENDUM

Since this paper was first submitted to the editor, we have treated 67 more cases of rheumatic disease with metacortandracin (Prednisone) or meta-cortandralone (Prednisolone). The results confirm those described above. We wish, however, to emphasize the possibility of deterioration on with-drawal. This was observed in three patients with rheumatoid arthritis after suspension of treatment. In these three patients the urinary excretion of 17-ketosteroids was lowered, so that the relapses may have been due to the inhibition of adrenal function.

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CHRONIC ARTHRITIS AFTER RECURRENT RHEUMATIC FEVER

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During the late 19th century the term "rheumatic fever" was applied to any case of acute febrile polyarthritis. In the past 50 years much evidence has been produced to support the view that rheumatic fever represents an abnormal tissue reaction to the products of Group A streptococcal infections (Poynton and Paine, 1913; Todd, 1932; Coburn and Pauli, 1935; Rothbard and others, 1948; Swift, 1952).

It is now recognized that rheumatoid disease may present as an acute febrile polyarthritis, but that this disease is not specially associated with streptococcal infection. Furthermore, in rheumatoid disease, there is a serum factor which forms the basis of the sheep cell agglutination test for this condition (Rose and others, 1948). This test gives negative results in patients with rheumatic fever. The older definitions of rheumatic fever as acute rheumatism and of rheumatoid disease as chronic rheumatism are no longer satisfactory, and it becomes desirable to know whether the rheumatic fever process may on occasion give rise to chronic joint disease.

Between 20 and 50 per cent. of patients with rheumatic fever eventually develop chronic heart disease (Edström, 1935; Coombs, 1924; Arnsø and others, 1951) and nearly all of them manifest one or more valvular lesions. The mitral valve is affected in 85 per cent., the aortic in 44 per cent., the tricuspid in 10 per cent., and the pulmonary in 1 or 2 per cent. (Cabot, 1926). It is generally agreed that the presence of a mitral lesion implies the existence of chronic heart disease resulting from a previous active rheumatic fever process. This observation is of some importance, as only 55 per cent. of cases of mitral stenosis give a history of the original attack (Parkinson and Hartley, 1946). As rheumatic fever commonly causes permanent changes in the heart, it is surprising that the present view of the complete reversibility of acute rheumatic polyarthritis is so widely accepted. One would expect a disease which attacks the cardiovascular and locomotor systems with equal frequency in its acute phase to produce permanent structural changes in both.

Follow-up studies of patients who had been treated for rheumatic fever have been carried out by a number of Scandinavian authors and some of them have reported chronic arthritis in 20 to 30 per cent. of their cases (Jespersen, 1941; Edström, 1935; Arnsø and others, 1951). Ehlertsen (1942), however, in a similar study was unable to confirm these findings. Unfortunately, these reports lack clinical detail and the incidence of chronic arthritis which they give is probably too high, as they all relate to a period when the term rheumatic fever was applied to any acute febrile polyarthritis.

Jaccoud (1869) gave the first detailed clinical description of chronic arthritis after rheumatic fever. This patient, a youth of 19, suffered from four attacks in which the hands and feet escaped, but in the course of which he developed aortic stenosis and incompetence. In two subsequent attacks deformities of the hands and feet, at first correctable but later permanent, appeared. There was marked ulnar deviation of the fingers and hyperextension of the middle on the proximal phalanx in the case of the second, third and fourth digits, unaccompanied by clinical evidence of bone destruction.

As the changes were situated chiefly in the joint capsules, he named the condition chronic fibrous rheumatism. Sporadic reports of similar cases have appeared in the literature, and Bywaters (1950) gives an excellent review of them. In addition he cites two cases of his own and in a study of autopsy material found joint changes which were possibly of the Jaccoud type in three out of five subjects with rheumatic heart disease.

* This work was carried out at the Rheumatism Research Centre, Manchester Royal Infirmary.

Involvement of the spine after rheumatic fever has been described from time to time in the literature. Poynton and Paine (1913) stated that the disease "may attack large as well as small joints, and may even in the young sometimes produce a very chronic spondylitis deformans". They considered that the likelihood of developing chronic arthritis increased with each succeeding attack. Krebs and Wurm (1938) were of the opinion that cardiac involvement was most frequently seen in those cases of spondylitis which follow rheumatic fever. The only patient with rheumatic heart disease among a small series of cases of ankylosing spondylitis described by Edström (1940) had suffered repeated attacks of rheumatic fever. In this case the *x*-ray changes in the spine and sacro-iliac joints were not typical of ankylosing spondylitis, and the condition underwent remission during treatment with salicylates. A somewhat similar case with atypical *x*-ray changes was mentioned by Herrick and Tyson (1941). Engleman and others (1951) found no peripheral joint changes among 137 veterans who had suffered from rheumatic fever during the second world war, but the existence of "rheumatoid spondylitis" in three of these patients was discovered by routine radiography of their sacro-iliac joints.

In a study of 352 cases of ankylosing spondylitis, Bernstein and Broch (1949) found valvular lesions in ten. They concluded that, in such cases, acute rheumatism should be regarded "as being part of the essential pathological picture presented by the patients". Recently the clinical and radiological features of ankylosing spondylitis have been more clearly defined (Mowbray and others, 1949; Hart and others, 1949), and Sharp and Easson (1954) have shown that only typical cases respond to radiotherapy. These authors suggest that atypical cases may result from involvement of the spine in other disease processes.

Bauer and others (1951) reported that the incidence of aortic regurgitation as a solitary lesion was higher among patients with rheumatoid arthritis than among a comparable group with rheumatic heart disease, indicating in their view, that aortic involvement is a manifestation of rheumatoid arthritis. Spinal involvement was a constant feature, but 75 per cent. had peripheral joint disease as well. Finally, Young and Schwedel (1944), in an account of 38 autopsies in patients with chronic arthritis, found valvular lesions of rheumatic origin in 24; fourteen had suffered from repeated attacks of acute polyarthritis, and in 23 there was evidence of spinal involvement.

Thus, from a study of the literature, there appears to be some association between recurrent rheumatic fever, valvular heart lesions, and an unusual form of chronic arthritis of which spondylitis is a prominent feature.

Present Study

Of all the patients who attended the Rheumatism Clinic at the Manchester Royal Infirmary between 1948 and 1953, 55 were recorded as having valvular disease of the heart, but only 28 of these were available for re-examination, together with the details of one fatal case.

These patients were re-investigated, special attention being paid to incidence of attacks of rheumatic fever, their relation to preceding infection and the effect of salicylates on the symptomatology and course of the disease. The character and pattern of joint involvement was noted, together with associated findings such as vasospasm and sweating of the extremities, tendon and subcutaneous nodules, atrophy of the skin and muscles and lymphadenopathy. All these cases had either a typical mitral presystolic or mid-diastolic murmur, or a to-and-fro aortic murmur, or both, and in most of them confirmatory radiological and electrocardiographic findings were available.

The following laboratory tests were carried out in most cases: erythrocyte sedimentation rate (Westergren with citrate anti-coagulant), differential sheep cell agglutination test (D.A.T.) by the method of Ball (1950), and antistreptolysin "O" titrations (A.S.T.) (Todd, 1932).

X-ray studies were confined to the affected joints in those patients who on the clinical assessment appeared to be suffering from rheumatoid arthritis. In the remainder, films of the hands, feet, pelvis, with special views of the sacro-iliac joints, and the whole of the spine were obtained.

Results

The main findings in these 29 patients are summarized in Table I (opposite).

Rheumatoid arthritis was diagnosed in those patients who presented a symmetrical polyarthritis affecting the small joints of the hands and feet, characterized by tender soft tissue thickening and limitation of the affected joints with radiological evidence of bone destruction as described by Fletcher and Rowley (1952). The frequent finding of vaso spasm and excessive sweating of the extremities, lymphadenopathy, necrobiotic nodules, and atrophic changes in muscle and skin supported this diagnosis. Cases 1 to 13 and also Case 19 fulfilled most of these criteria. Aspirin in a dosage of 60 gr. or more daily produced moderate relief of joint

TABLE I

MAIN FINDINGS IN 29 PATIENTS

Case No.	Sex	Age	Duration (yrs)	No. of Attacks of Rheumatic Fever	Aspirin Response	Peripheral Joints		Central Joints		Differential Sheep Cell Agglutination Test	Erythrocyte Sedimentation Rate	Antistreptolysin Titration	Heart Lesion
						Clinical	*X*-Ray	Clinical	*X*-Ray				
1	F	51	32	0	+	R.A.	R.A.	Cervical	nil	+	12	50	Mitral
2	F	54	20	0	++	R.A.	R.A.	nil	nil	+	8	25	Mitral
3	F	44	2	0	++	R.A.	R.A.	nil	nil	+	47	50	Mitral
4	F	44	5	0	++	R.A.	R.A.	nil	nil	+	6	50	Mitral
5	F	54	5	0	+	R.A.	R.A.	nil	nil	+	20	100	Mitral, aortic
6	F	70	20	0	+	R.A.	R.A.	Cervical	nil	+	83	50	Mitral, aortic
7	F	54	10	0	+	R.A.	R.A.	Cervical	nil	+	55	50	Aortic
8	M	39	5	1	++	R.A.	R.A.	Cervical	nil	+	27	1,600	Mitral, aortic
9	M	55	3	2	++	R.A.	R.A.	nil	nil	+	40	100	Mitral
10	M	53	10	1	++	R.A.	R.A.	Cervical	nil	+	3	25	Mitral
11	F	18	6	1	++	R.A.	R.A.	nil	nil	—	19	150	Mitral, aortic
12	F	45	3	1	+	R.A.	nil	nil	nil	—	10	150	Mitral
13	F	47	3 mths	1	++	R.A.	nil	nil	nil	—	22	100	Mitral
14	F	20	5	1	+++	Indeterminate	nil	nil	nil	—	2	260	Mitral
15	M	23	3	1	++	nil	nil	Lumbo-dorsal	Typical spondylitis (Fig. 4)	—	5	100	Aortic
16	M	62	10	2	++	nil	Healed osteoporosis wrists	Lumbo-dorsal	Spondylitis	—	47	50	Mitral
17	M	47	4	0	+++	nil	nil	Lumbo-dorsal	Spondylitis	—	42	100	Mitral, aortic
18	M	31	4	0	+++	Indeterminate	Healed osteoporosis feet	Lumbo-dorsal	Spondylitis	—	35	100	Mitral, aortic
19	F	33	4	3	++	R.A.	Juxta articular porosis only	nil	nil	—	22	130	Mitral, aortic
20	F	26	2	3	+++	Effusions hypermobility	nil	nil	nil	—	20	150	Mitral, aortic
21	F	46	18	3	++	Effusions nodules	nil	nil	nil	—	10	25	Mitral
22	M	38	8	4	+++	Effusions only	nil	Lumbo-dorsal	Spondylitis	—	50	not done	Mitral, aortic
23	M	41	2	3	+++	Stiff shoulders	nil	Lumbo-dorsal	Fused sacro-iliac joints	—	2	not done	Mitral, aortic
24	M	48	9	4	+++	Stiff shoulders	nil	Lumbo-dorsal	Spondylitis	—	18	130	Aortic
25	M	42	16	5	+++	nil	nil	Lumbo-dorsal	Spondylitis	—	10	130	Mitral, aortic
26	M	29	10	5	+++	Hypermobility	nil	Lumbo-dorsal	Spondylitis	—	1	100	Mitral, aortic
27	M	35	20	6	+++	Hypermobility Effusions Nodules	Osteoporosis (Fig. 1*b*)	Whole spine	Spondylitis (Figs. 1*a*, 2, 3)	—	40	1,100	Mitral, aortic
28	F	39	20	3	+++	Hypermobility	nil	Whole spine	Spondylitis	—	25	100	Mitral
29	F	25	15	5	+++	Hypermobility Nodules	Osteoporosis	Lumbo-dorsal	Erosions sacro-iliac joints	—	40	800	Mitral, aortic

symptoms in no way comparable to the striking effect obtained in rheumatic fever. Spinal arthritis was limited to the cervical region and in most cases there were confirmatory radiographical changes in the hands and feet consisting of juxta-articular osteoporosis and erosions. All, with one exception, were considered to have involvement of the mitral valve. The exception, a woman aged 54, did not give any previous history of rheumatic fever or symptoms which could be ascribed to a cardiovascular disorder. Her severe destructive rheumatoid arthritis of 10 years' duration had confined her

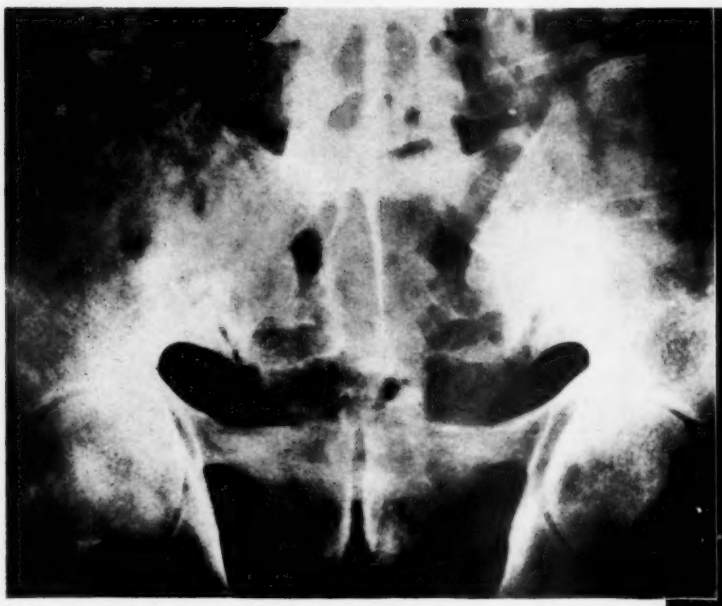

Fig. 1(*a*).—Case 27. Table I.

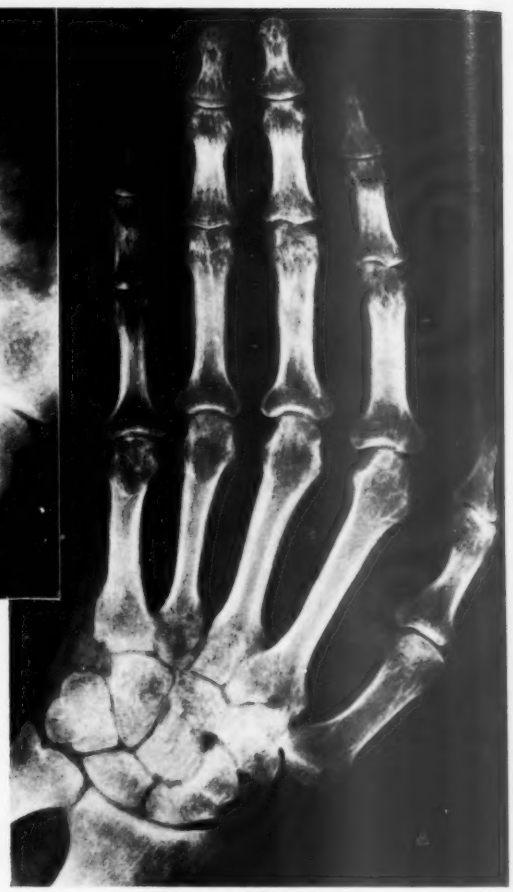

Fig. 1(*b*).—Case 27. Table I.

to bed for 7 yrs and was possibly the cause of her aortic incompetence. The differential sheep cell agglutination test was positive in ten of these cases.

Cases 19 to 29 complained of recurrent attacks of febrile polyarthritis, and nine stated that these attacks were invariably preceded by episodes suggestive of upper respiratory infection. Aspirin in doses of 60 gr. or more daily appeared to control joint pains and fever when present, though in patients with ankylosed spines mobility was naturally not restored. Thus the therapeutic response was of the order one would expect in patients with rheumatic fever.

Ten of these patients showed changes in the peripheral joints, but in only one could these be described as typical of rheumatoid arthritis. Two displayed moderate limitation of movement in the shoulders only. Hypermobility, particularly of the metacarpophalangeal joints of the hands, was found in Case 20 and Cases 26-29: it arose from laxity of the ligaments and capsules which permitted a considerable degree of ulnar deviation, but no actual dislocations (Fig. 1*b*).

Additional findings included effusions into the metacarpophalangeal joints and extensor tendon sheaths at the wrists and tendon nodules, which in one case had produced bilateral compressions of the median nerves in the carpal tunnels (Case 21).

In eight of the patients in this group there was gross limitation of movement of the lumbodorsal spine (Cases 22-29 inclusive), and in two of them the whole spine was virtually ankylosed. Three patients had deep *x*-ray therapy applied to the spine, but in no case was this followed by any symptomatic improvement.

The *x* rays of the hands and feet in these patients did not reveal any erosions of the rheumatoid type. In one patient (Case 19) there was juxta-articular porosis only, and Cases 27 and 29 showed in addition a curious alteration of the bone trabecular pattern (Fig. 1*b*). *X* rays of the sacro-iliac joints showed complete fusion in one patient. In seven there were abnormalities unlike those usually seen in ankylosing spondylitis consisting of very small erosions surrounded by spotty areas of sclerosis (Fig. 1*a*). The radiological changes in their spines consisted of irregularity and fusion of the interfacetal joints, narrowing of the intervertebral discs, increased height of the vertebral bodies, and some ossification in the discs; appearances which are unlike those of typical ankylosing spondylitis (Figs 2 and 3).

Isolated aortic valve disease was encountered in

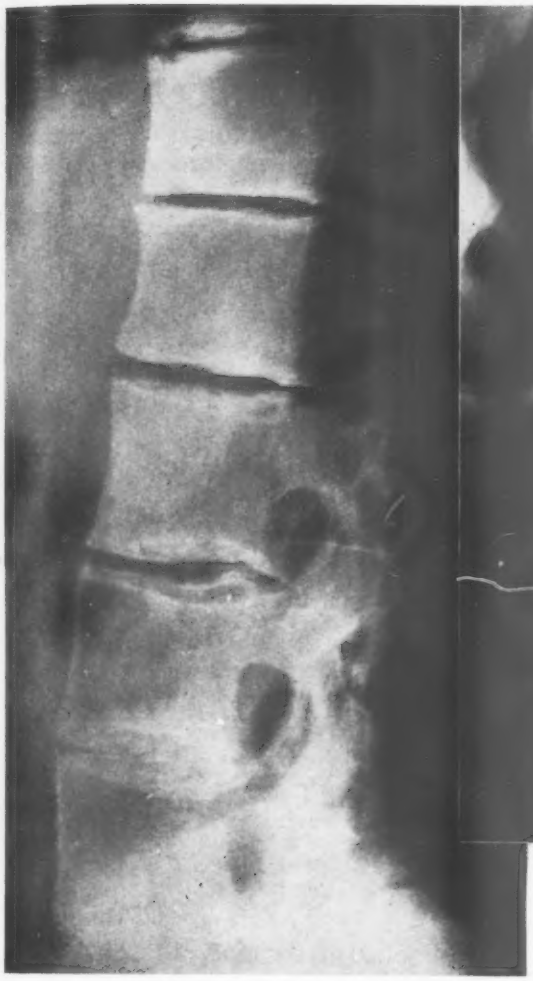

Fig. 2.—Case 27. Table I.

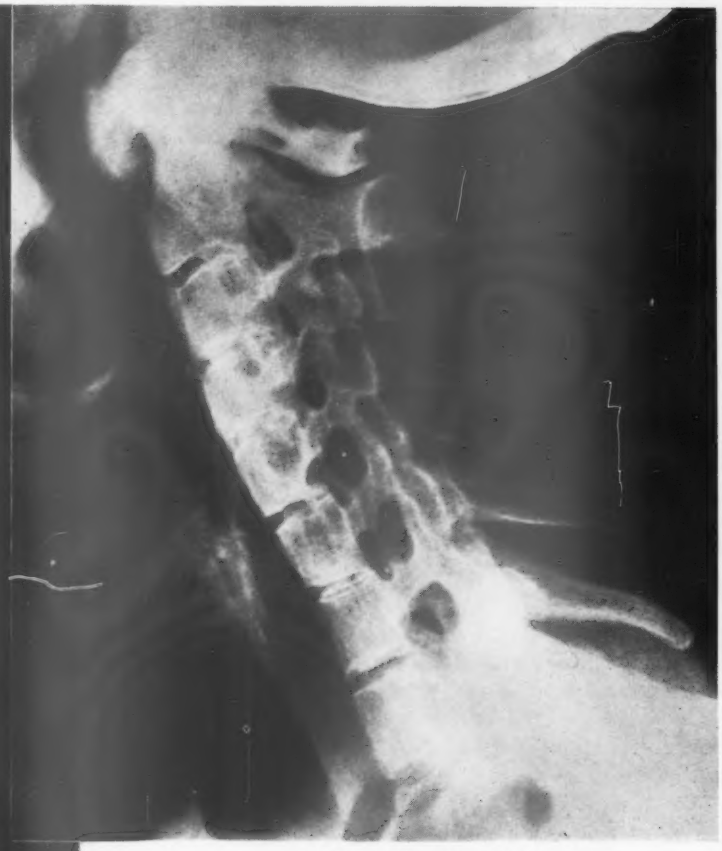

Fig. 3.—Case 27. Table I.

one patient only (Case 24), and as this lesion had developed during one of a series of attacks of rheumatic fever, it was considered to be rheumatic in origin.

The differential sheep cell agglutination test was negative in all the patients in this group. Anti-streptolysin "O" titrations were performed in the hope that they might provide some evidence of continuing rheumatic activity when this was present. Todd (1932) and Swift (1952) have shown, however, that whilst high titres may be obtained in the early stages of an attack of rheumatic fever, the level falls rapidly as the illness proceeds and is usually normal during the inactive stages. The two patients with high titres in this group were both seen during an acute attack.

The remaining five patients (Cases 14 to 18 inclusive) formed a heterogeneous intermediate group consisting of:

Case 14.—A girl aged 20 developed mitral stenosis after an attack of rheumatic fever when she was 16, which was preceded for twelve months by arthritis of the hands and feet. The polyarthritis was not progressing at the time of examination and the joint changes were indeterminate in nature, comprising soft tissue thickening of the ankles only.

Case 15.—A man aged 23 was considered to have inactive ankylosing spondylitis. The *x*-ray appearances of his sacro-iliac joints—big erosions and large fluffy areas of sclerosis—were typical (Fig. 4, overleaf). He had derived great benefit from radiotherapy. His isolated aortic lesion was regarded as rheumatic in origin in view of his previous history of rheumatic fever.

Case 16.—A man aged 62 who, 10 years after a second attack of rheumatic fever, developed progressive stiffness of the lumbodorsal spine. Radiographs of the sacro-iliac joints disclosed changes similar to those described above in the patients with recurrent rheumatic fever. He also responded to radiotherapy.

Cases 17 and 18.—These differed from the patients with recurrent rheumatic fever and stiffness of the lumbo-dorsal spine only by the absence of a history of repeated attacks.

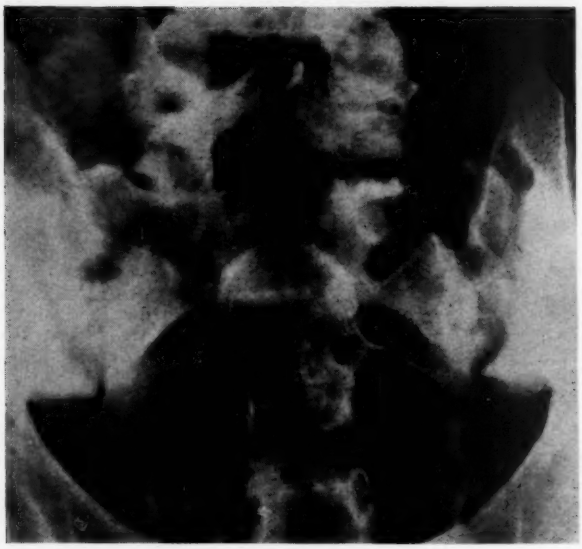

Fig. 4.—Case 15 Table I.

Table II (opposite) contains details from the case notes of the 26 patients who did not attend for re-examination. Cases 1-6 inclusive were thought to have rheumatoid arthritis; excepting Case 6 with congenital pulmonary stenosis, their valve lesions were considered to be rheumatic in origin.

Case 7 had, for a number of years, complained of attacks described as "asthma". During the course of her illness she developed an arthritis of the rheumatoid type, arteritis of the digital arteries, and aortic incompetence. She was considered on clinical grounds to have periarteritis nodosa.

Frequent bouts of iritis after urethritis during the first world war preceded the polyarthritis in Case 11 who was thought to have Reiter's disease. The aetiology of his aortic incompetence was never established.

The remaining patients were all suffering from rheumatic heart disease, and seven of them (Cases 20-26) displayed joint changes of the type previously described as possibly due to the rheumatic process. Limitation of movement in the lumbodorsal spine was a feature in three of these patients of whom two showed accompanying changes in the peripheral joints.

Valvular heart disease was encountered in nineteen of 1,562 patients (1·2 per cent.) with rheumatoid arthritis seen during the 5-year period of the survey. In sixteen (1 per cent.), the valvular lesions were of rheumatic origin, a smaller clinical incidence than the 4 per cent. reported by Sokoloff (1953).

490 patients with spondylitis were seen during the same period and sixteen of these had valve lesions (3·3 per cent.), of which fifteen (3·1 per cent.) were rheumatic. Bernstein and Broch (1949) encountered rheumatic heart disease in 2·8 per cent. of their 352 cases of ankylosing spondylitis.

Discussion

Both rheumatoid arthritis and rheumatic heart disease are common conditions. The association between them encountered in this study is not unexpected and probably represents no more than a chance occurrence of two diseases in the same patient.

Joint changes seen in the patients who had suffered repeated attacks of rheumatic fever were similar in many respects to those described by Jaccoud (1869), but in a lesser degree, the lesions being confined to the joint capsules and tendons. It was in these structures that Klinge (1933) found the most marked histological changes in a patient dying of rheumatic fever.

A number of patients in the series were drawn from a clinic for the diagnosis of ankylosing spondylitis, a fact which may account for the high incidence of spinal involvement. There seemed, however, to be certain differences between these patients and typical cases of ankylosing spondylitis, notably the history of repeated attacks of rheumatic fever, absence of focal points, presence of tendon nodules, and differing radiographic changes in the sacro-iliac joints. Furthermore, in five cases, the spondylitis was associated with peripheral joint changes of the Jaccoud type (Table I, Cases 26 to 29 inclusive; Table II, Case 24).

Recurrent attacks of rheumatic fever continuing into adult life are distinctly uncommon, and the cases reported in this paper represent the only patients seen in this clinic in whom this diagnosis has been considered likely. Although the evidence is incomplete in that we have no bacteriological proof of preceding streptococcal infection (except in Case 27, Table I), and the Antistreptolysin Titrations are also unhelpful, the frequent history of preceding infection, the striking response to salicylates, and the curious nature of the joint lesions, suggest that at least seventeen of these patients were, in fact, suffering from recurrent rheumatic fever. It is interesting that the heart disease in these seventeen patients tended to be more severe and progressive than in the series as a whole.

If we accept the view that these patients are suffering from recurrent rheumatic fever, it raises the possibility that their joint lesions may be due to the rheumatic fever process. Alternatively, some of these patients might be suffering from a recurrent, acute febrile form of ankylosing spondylitis with cardiac involvement or simply a coincident ankylosing spondylitis and recurrent rheumatic fever. Further resolution of this problem must await bacteriological and serological studies of this type of case during the acute episodes, but for the moment,

TABLE II
FINDINGS IN 26 PATIENTS

Case No.	Sex	Age	Duration (yrs)	No. of Attacks of Rheumatic Fever	Peripheral Joints		Central Joints		Differential Sheep Cell Agglutination Test	Erythrocyte Sedimentation Rate	Heart Lesion
					Clinical	*X*-Ray	Clinical	*X*-Ray			
1	F	25	10	0	R.A.	R.A.	nil	Not done	+	40	Mitral
2	F	38	11	1	R.A.	R.A.	nil	Not done	—	25	Mitral
3	F	55	15	0	R.A.	R.A.	Cervical	Not done	+	30	Mitral, aortic
4	F	46	5	1	R.A.	R.A.	nil	Not done	Not done	56	Mitral
5	F	44	2	0	R.A.	R.A.	nil	Not done	+	40	Mitral
6	F	37	15	0	R.A.	R.A.	Cervical	Not done	+	40	Congenital pulmonary stenosis
7	F	30	10	0	R.A.	R.A.	nil	Not done	—	50	Aortic
8	F	57	5	0	Osteo-arthritis knees Obesity	Osteo-arthritis	nil	Not done	Not done	5	Aortic
9	F	45	2 mths	0	Occupational lesion to elbow	nil	nil	Not done	Not done	10	Mitral
10	F	62	5	0	nil	Not done	Low back pain	Pseudo-spondylolisthesis	Not done	Not done	Mitral
11	M	57	3	0	Soft tissue Swelling of knees and feet	Erosions of metatarsal heads	Lumbo-dorsal	Abundant lipping	—	50	Aortic
12	M	32	6 mths	3	Arthralgia	nil	nil	Not done	—	5	Mitral, aortic
13	M	18	9 mths	1	Arthralgia	nil	nil	Not done	—	5	Mitral, aortic
14	F	42	Not known	6	Painful stiff shoulders	nil	nil	Not done	Not done	30	Mitral, aortic
15	M	40	Not known	2	Arthralgia	nil	nil	Not done	Not done	9	Mitral
16	F	34	1	1	Arthralgia	nil	nil	Not done	Not done	22	Aortic
17	M	50	3 mths	1	Arthralgia in attack of rheumatic fever	nil	nil	nil	Not done	65	Mitral, tricuspid
18	F	37	1 mth	3	Effusions knees in attack of rheumatic fever	nil	nil	Not done	Not done	98	Mitral, aortic
19	F	22	2 mths	1	Swollen tender ankles in attack of rheumatic fever	nil	nil	Not done	Not done	50	Apical systolic murmur only
20	F	40	6 mths	3	Nodules both tendo-achilles	nil	nil	Not done	—	15	Mitral
21	F	39	1	3	Effusions small joints of hands	Erosions of metacarpal heads	nil	Not done	Not done	53	Mitral
22	F	38	Not known	6	Hypermobility small joints of hands Subluxations	nil	nil	Not done	—	13	Mitral
23	F	37	6 mths	3	Tendon nodules	nil	nil	Not done	—	15	Mitral
24	F	50	1	2	Hypermobility small joints of hands Subluxations	nil	Lumbo-dorsal	nil	Not done	25	Mitral
25	M	47	6 mths	6	Effusions knees Soft tissue thickening	nil	Lumbo-dorsal	nil	—	30	Aortic
26	M	33	13	2	Limitation hands nil	nil	Whole spine	Spondylitis	—	31	Aortic ? mitral

the practical management appears to be that of recurrent rheumatic fever.

Summary

(1) Clinical, radiological, and serological data from a group of patients with chronic arthritis and rheumatic heart disease were analysed.

(2) An expected association between rheumatoid arthritis and rheumatic heart disease was encountered.

(3) A group of patients with recurrent febrile polyarthritic episodes, valvular heart disease, atypical spondylitis, and peripheral joint changes of the Jaccoud type is described.

(4) In this group the attacks of polyarthritis were often preceded by upper respiratory infection and salicylate therapy provided a most effective method of controlling the symptoms.

(5) The significance of these findings is discussed.

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L'arthrite chronique après le rheumatisme articulaire aigu

RÉSUMÉ

(1) On analysa les données cliniques, radiologiques et de laboratoire chez un groupe de malades atteints d'arthrite chronique et de maladie de Bouillaud.

(2) Comme on s'y attendit, on trouva un rapport entre l'arthrite rhumatismale et la maladie de Bouillaud.

(3) On décrit un groupe de malades manifestant des épisodes polyarthritiques fébriles, une atteinte valvulaire du coeur, une spondylarthrite atypique et des altérations articulaires périphériques de type Jaccoud.

(4) Dans ce groupe les poussées articulaires furent souvent précédées d'infections des voies respiratoires supérieures et la thérapie salicylée s'avera la plus efficace pour obtenir un soulagement symptomatique.

(5) On discute la portée de ces résultats.

La artritis crônica después del reumatismo poliarticular agudo

SUMARIO

(1) Se analizaron los datos clínicos, radiológicos y serológicos en un grupo de enfermos con artritis crónica y con reumatismo poliarticular agudo.

(2) Se encontró la anticipada asociación entre la artritis reumatoide y el reumatismo poliarticular agudo.

(3) Se describe un grupo de enfermos manifestando episodios poliartríticos febriles, una enfermedad valvular del corazón, una espondilartritis atípica y alteraciones articulares periféricas de tipo de Jaccoud.

(4) En este grupo ataques articulares fueron a menudo precedidos de infecciones de las vías respiratorias superiores y la terapia salicilada se mostró la más eficaz para controlar los síntomas.

(5) Se discute el significado de estos datos.

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SERUM DIPHENYLAMINE REACTION IN RHEUMATOID ARTHRITIS

BY

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Normal human serum in contact with Dische's diphenylamine reagent produces a reddish-purple colour; this is increased in such conditions as cancer, pulmonary tuberculosis, and rheumatic fever (Niazi and State, 1948). According to Coburn and others (1953) and Coburn and Haninger (1954), connective tissue is a rich source of the diphenylamine-reactive substance, the concentration of which in the blood stream as detected by the diphenylamine reaction increases principally during a sterile inflammatory reaction and appears to be conditioned by the intensity of the inflammatory process. In rheumatic fever, the diphenylamine reaction is much more intense in the acute phase, decreases with the lessening of the symptoms, and returns to normal with their subsidence; it parallels in most cases the erythrocyte sedimentation rate; it is inhibited by "antiphlogistic" drugs, such as salicylates, cortisone, and hydrocortisone (Ayala, Moore, and Hess, 1951). Therefore serial diphenylamine determinations are helpful both in estimating the degree of rheumatic activity and in evaluating the efficacy of therapeutic agents.

The substance in the serum which reacts with diphenylamine to produce the purple colour has not been certainly identified. It may be a mucoprotein, with a very low iso-electric point (less than 2), the reddish-purple colour being due to the carbohydrate of the mucoprotein found in the α-globulin fraction.

The present report includes a study of the diphenylamine values in thirty patients with rheumatoid arthritis, comparing the variations with changes in the clinical picture and erythrocyte sedimentation rate (Westergren measurements at one hour). The values in eight cases of ankylosing spondylitis, and one case of acute disseminated lupus erythematosus are also included.

Method

The technique used was the semimicro-procedure described by Ayala, Moore, and Hess (1951).

The readings were made with the Unicam spectrophotometer, model SP 350, with a wave length of 530 mμ, using ½-in. test-tubes. The results are calculated in colorimetric units (log. I°/I).

Our normal values differ from those of Ayala, Moore, and Hess (1951) who used a Coleman spectrophotometer, model 6A. We have therefore established our own "normal" values, using the serum of thirty individuals with no acute disease. The optical density obtained ranged from a maximum of 0·140 to a minimum of 0·120, with a mean of 0·134 and a maximum variation of 0·020 units. These figures were used as our basic values.

Results

The diphenylamine reaction was studied in thirty patients with rheumatoid arthritis, of whom eight were in the third and fourth stages,* and 22 in the first and second stages.*

In the first group (three men and five women between the ages of 25 and 65), colorimetric values within normal limits were constantly found, that is from 0·120 to 0·140 (mean 0·134); the erythrocyte sedimentation rate was also within normal limits (Table I).

TABLE I
DIPHENYLAMINE REACTION AND E.S.R. DETERMINATIONS IN EIGHT PATIENTS WITH RHEUMATOID ARTHRITIS IN STAGES III AND IV

Sex	Age	Erythrocyte Sedimentation Rate	Diphenylamine Reaction
m	56	8	0·125
m	40	12	0·133
m	65	25	0·120
f	32	36	0·137
f	30	10	0·140
f	28	5	0·130
f	43	19	0·127
f	39	21	0·143

* Steinbrocker, Traeger, and Battermann (1949).

TABLE II

SERIAL DIPHENYLAMINE REACTION AND E.S.R. DETERMINATIONS IN 22 PATIENTS WITH RHEUMATOID ARTHRITIS IN STAGES I AND II

Sex	Age	Before Treatment		After 30 days		Grade of Improvement	Treatment
		Erythrocyte Sedimentation Rate	Diphenylamine Reaction	Erythrocyte Sedimentation Rate	Diphenylamine Reaction		
m	25	36	0·183	14	0·132	II	x
f	38	26	0·189	6	0·125	II	x
m	40	48	0·155	9	0·140	II	x
m	41	31	0·245	10	0·137	II	x (Fig. 2*a*)
m	26	36	0·175	5	0·133	I	x
f	29	45	0·200	6	0·140	I	x (Fig. 2*b*)
f	45	40	0·185	13	0·132	II	x
m	30	31	0·190	14	0·140	II	x
m	28	37	0·198	10	0·119	II	x
f	40	31	0·170	9	0·121	I	xxx
m	34	48	0·158	12	0·131	II	xxx
m	26	32	0·191	14	0·131	II	xxx
m	29	30	0·178	21	0·140	II	x
f	27	33	0·240	42	0·131	II	x (Fig. 2*c*)
m	45	85	0·201	27	0·130	I	xx
m	32	101	0·168	44	0·128	II	xx
f	41	52	0·173	40	0·138	II	xx
m	34	72	0·220	45	0·142	II	xx
m	27	35	0·222	30	0·170	III	xx (Fig. 2*d*)
f	32	53	0·183	48	0·175	IV	xx
m	30	62	0·202	30	0·178	III	xx
m	43	45	0·165	37	0·158	III	xx

Average Daily Doses { x = 44 mg. hydrocortisone by mouth. xx = 450 mg. phenylbutazone by mouth. xxx = 250 mg. phenylbutazone and 35 mg. hydrocortisone by mouth.

In the second group (fifteen males and seven females between the ages of 25 and 45), the course of the reaction was studied for a period of 30 days, determinations being done every 10 days (Fig. 1).

During this period the patients were under treatment with phenylbutazone by mouth, or hydrocortisone, or a combination of both. The dosage is set out in Table II, which also includes the values obtained at the beginning and end of the investigation.

At the beginning of our observations the colorimetric values of the diphenylamine reaction were consistently high in all patients (maximum 0·245, minimum 0·155, mean 0·190). On the 30th day the colorimetric values had fallen to normal in eighteen patients (above the continuous line in Table II; maximum 0·140, minimum 0·119, mean 0·132); the values remained above normal in four (below the continuous line in Table II; maximum 0·178, minimum 0·158, mean 0·170).

On the 30th day the erythrocyte sedimentation rate, which was high in all at the beginning of the testing period, had fallen to normal in twelve patients (above the dotted line in Table II, *e.g.* Figs 2*a* and *b*).

The course of the diphenylamine reaction was parallel to that of the clinical condition; that is the eighteen patients in whom the values returned to normal within 30 days all presented a Grade I or II improvement, while the other four were Grade III and IV.

The erythrocyte sedimentation rate remained high in six of the eighteen patients in whom the diphenylamine reaction had become normal (between the dotted and continuous lines in Table II, *e.g.* Fig. 2*c*).

The diphenylamine reaction returned to normal in all patients treated with hydrocortisone (*e.g.* Figs 2*a*, *b*, *c*), in all those treated with hydrocortisone and phenylbutazone, and in four of those treated with phenylbutazone only. The four patients in whom the diphenylamine reaction was

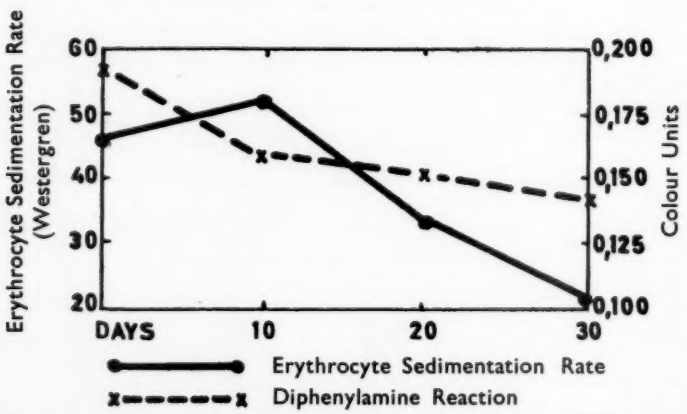

Fig. 1.—Relation of diphenylamine reaction and erythrocyte sedimentation rate in 22 patients with rheumatoid arthritis.

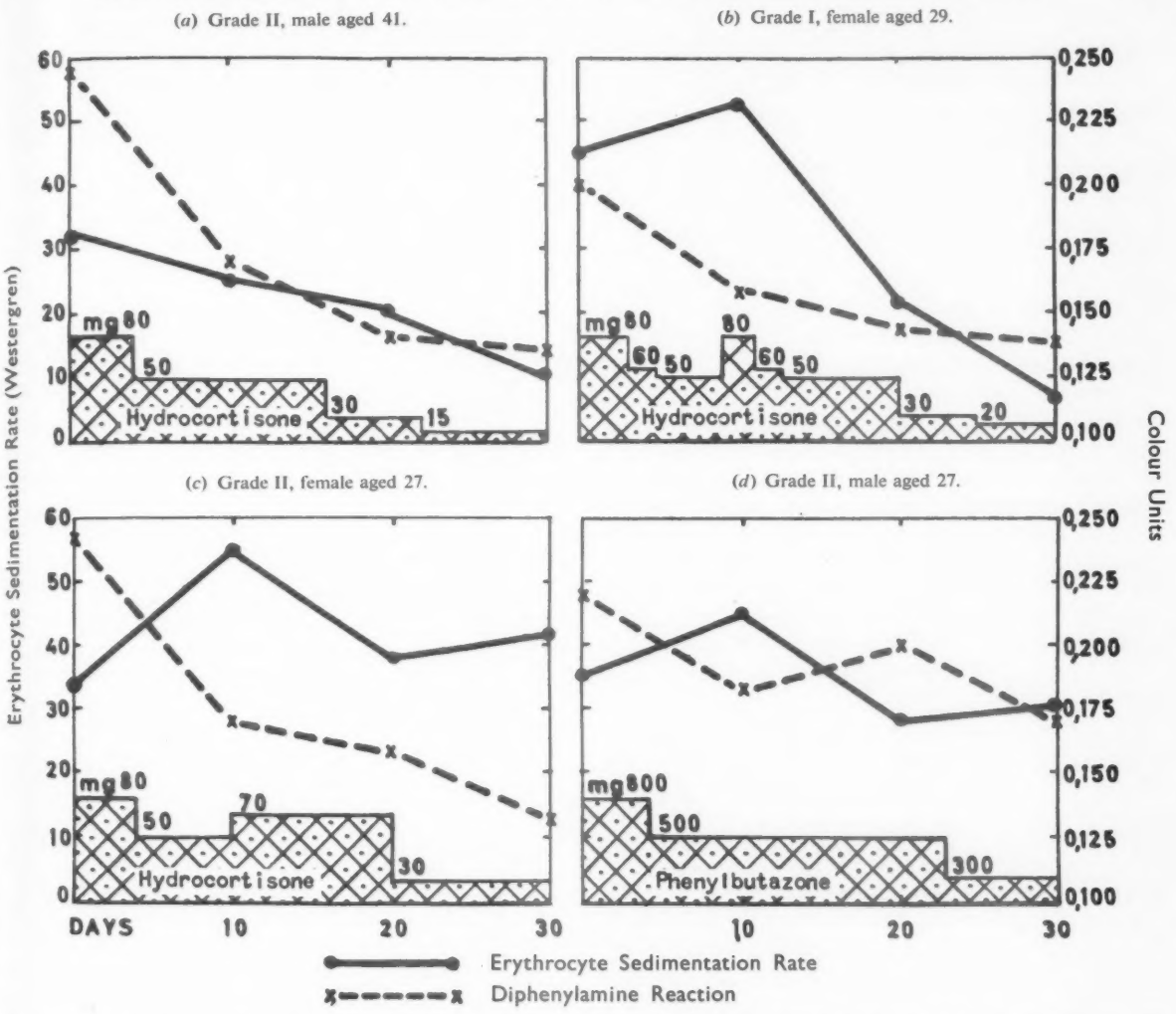

Fig. 2.—Diphenylamine reaction and erythrocyte sedimentation rate in four cases of rheumatoid arthritis (cf. Table II), showing sex, age, dosage, and grade of improvement.

higher than normal at the end of 30 days (below continuous line in Table II) had been treated with phenylbutazone alone (*e.g.* Fig. 2*d*).

In seven cases of ankylosing spondylitis (six males and one female, aged from 18 to 55), of whom two were in the relatively early stages (that is approximately 1 year from the onset of sacro-iliac and vertebral symptoms), moderately raised colorimetric values were found only in the two early cases. The values of 0·174 and 0·169 in these two patients (above the line in Table III) corresponded to a moderate rise in the sedimentation rate.

In one 18-year-old female patient with acute lupus erythematosus, continuous and very high levels were found (from 0·278 to 0·295) at monthly intervals; they did not correspond to the clinical picture, and were unaffected by the administration of therapeutic agents.

TABLE III

SERIAL DIPHENYLAMINE REACTION AND E.S.R. DETERMINATIONS IN SEVEN PATIENTS WITH ANKYLOSING SPONDYLITIS

Sex	Age	Before Treatment		After 30 days	
		Erythrocyte Sedimentation Rate	Diphenylamine Reaction	Erythrocyte Sedimentation Rate	Diphenylamine Reaction
m	18	29	0·174	38	0·140
m	22	19	0·169	32	0·135
m	45	8	0·128	8	0·130
m	38	12	0·132	10	0·135
m	27	18	0·125	11	0·122
m	23	7	0·140	22	0·139
f	53	16	0·138	15	0·130

Comment

This subject, which is still in its infancy but is full of scientific and practical interest in face of the specific immunological reactions caused by bacterial and virus infections, concerns the non-specific reactions not bound to anti-body production, which appear in the blood stream during the acute phase of infections. Reactions similar to the raising of the erythrocyte sedimentation rate occur even during non-infectious diseases and tend to persist in the blood as long as the disease remains active. They probably result from enzymatic adjustments which produce symptoms, anatomical changes, and finally recovery from the disease.

Among these acute-phase reactions, a particular significance seems to belong to the concentration in the blood of a diphenylamine-reactant substance; its exact chemical composition is not yet known, but it is probably a serum muco-protein. Recent studies of rheumatic fever have shown that the diphenylamine reaction is a valuable aid in determining the degree of activity of the disease and the efficacy of the drugs used in treating it.

Our research has shown that this reaction may also be used to test the course of rheumatoid arthritis; the diphenylamine reaction is constantly increased during the active phases of the disease and follows the clinical variations more faithfully and promptly than the erythrocyte sedimentation rate. Even though the absolute colorimetric value is not proportional to the gravity of the disease, it does show very clearly the degree of rheumatoid activity. It is less useful in diagnosis because it is also raised in other conditions, including rheumatic fever and disseminated lupus erythematosus, and is not sufficiently indicative in ankylosing spondylitis.

A most interesting feature was the rapidity with which the serum concentration of the diphenylamine-reactant substance fell with the use of hydrocortisone. This change was less marked with phenylbutazone.

Summary

The behaviour of the diphenylamine reaction is compared with that of the erythrocyte sedimentation rate in thirty cases of rheumatoid arthritis and seven of ankylosing spondylitis in various stages. The values found in the normal individual average 0·134 units with a maximum of 0·140 and a minimum of 0·120 (Unicam spectrophotometer, SP 350).

In active cases of rheumatoid arthritis (Stages I and II) these values were found to be constantly increased (mean 0·190), and tended to return to normal with improvement in the clinical picture; the reaction also seemed to be influenced by therapy, especially by hydrocortisone. As a measure of disease activity and of the efficacy of the therapy adopted, the reaction appears to be in general more sensitive than the erythrocyte sedimentation rate.

No significant alteration from normal was encountered in cases of rheumatoid arthritis in Stages III and IV or in ankylosing spondylitis.

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La réaction sérique de diphénylamine dans l'arthrite rhumatismale

Résumé

On compare le comportement de la réaction de diphénylamine à celle de la sédimentation globulaire dans trente cas d'arthrite rhumatismale et sept cas de spondylarthrite ankylosante aux diverses états de la maladie. Chez des sujets normaux o trouva le chiffre moyen de 0,134 unités, avec un maximum de 0,140 et un minimum de 0,120 (spectrophotomètre Unicam, Model SP 350).

Dans les cas d'arthrite rhumatismale active (états I et II), ces chiffres augmentaient constamment (moyenne de 0,190) et tendaient à revenir à la normale avec l'amélioration du tableau clinique; cette réaction semblait également subir l'influence du traitment, surtout par l'hydrocortisone. En tant que mesure de l'activité morbide et de l'efficacité du traitement adopté, cette réaction parait être, en général, plus sensible que la sédimentation globulaire.

On n'a pas trouvé de déviations significatives dans des cas d'arthrite rhumatismale aux états III et IV ou des cas de spondylarthrite ankylosante.

La reacción sérica de difenilamina en la artritis reumatoide

Sumario

Se compara el comportamiento de la reacción de difenilamina con la de la sedimentación eritrocitaria en treinta casos de artritis reumatoide y siete casos de espondilartritis anquilosante en varios períodos de la enfermedad. En sujetos normales se encontraron valores medios de 0,134 unidades, con un máximo de 0,140 y un mínimo de 0,120 (espectrofotometro Unicam, Model SP 350).

En los casos de artritis reumatoide activa (período I y II) estos valores aumentaban constantemente (en promedio 0,190) y tendían a normalizarse con la mejoría del cuadro clínico; esta reacción parecía también estar bajo la influencia del tratamiento, particularmente de la hidrocortisona. Como medida de la actividad mórbida y de la eficacia del tratamiento elegido, esta reacción parece, en general, más sensible que la sedimentación globular.

No se encontraron desviaciones significativas en los casos de artritis reumatoide en períodos III y IV ni en los de espondilartritis anquilosante.

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RHEUMATOID ARTHRITIS AND PLASMACYTOMATOSIS

BY

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The importance of plasma disorders in the diagnosis and pathogenesis of rheumatoid arthritis is well known. Galli and others (1949a, b, c) have studied the erythrocyte sedimentation rate, the occurrence of amyloidosis, and the alteration of the protein composition of plasma, and examined the inter-relations of plasma disorders with the signs and symptoms of rheumatoid arthritis.

It was concluded that an increase in the erythrocyte sedimentation rate was a sign not only of an inflammatory state involving the joints, but also of a pathological systemic condition. The correlation of the erythrocyte sedimentation rate with plasma protein production suggested that alterations in the latter were phenomena of the disease process.

The amyloidosis studies led to the assumption that a fault in the mesenchyma might cause changes in blood and tissue protein metabolism.

Blood-protein disorders were shown to play a part in the pathogenesis of rheumatoid arthritis which was linked with the state of the plasma proteins.

Chini (1955) has discussed a new type of joint pathology, which he calls "dysprotidaemic joint disease". This conception arose from the frequency of plasma cell and reticulo-endothelial proliferation in rheumatoid arthritis, the frequent concomitant amyloidosis, and the evidence of joint damage in such blood-protein disorders as myeloma, and primary and secondary amyloidosis. The histiocytic hyperplasia inside and outside the bone marrow, which has been demonstrated in rheumatoid arthritis, suggests that a systemic histioplasmacytic hyperplasia occurs in this condition.

These data suggest that anomalous protein production takes place at the sites of plasma cell proliferation (Poli, 1948, 1949; Redaelli and Gianni, 1949; and Vidari, 1941, 1946).

There is evidence of joint damage in myeloma, with accumulation of amyloid substance in the articular tissues (Delbarre, 1949; Laake, 1949; Magnus-Levy, 1932, 1938; Snapper, 1938; Stadler, 1939; Weissenbach and Faulong, 1948); the main joints are usually involved (Apitz, 1940a, b; Delbarre, 1949); the condition resembles arthrosis (Stadler, 1939), though more joints may be affected, and appears to be similar to rheumatoid arthritis. Delbarre speaks of "amyloid rheumatism" (Apitz, 1940a, b; Stewart and Weber, 1938; Tarr and Ferris, 1939; Weissenbach and Faulong, 1948).

According to Chini (1955), the articular involvement may imply a multiple pathogenic mechanism:

(1) contiguous diffusion of myelomatous bone damage;
(2) amyloid accumulation in articular tissues;
(3) systematized involvement of the histiocytic joint tissues by the myelomatous process, with precipitation of abnormal proteins into the articular tissues;
(4) secondary histogenetic reaction inducing granulomatous and fibrous processes.

Little is known of articular involvement in classical secondary amyloidosis (Cesa-Bianchi and Poli, 1948; Lengh, 1937). Joint lesions are seldom found in systemic primary amyloidosis (Bonsdorff, 1934; Dahlin, 1949; Lengh, 1937; Lubarsch, 1929; Ronchetti, 1930; Stadler, 1939). Articular manifestations of blood protein disorders, other than myeloma and amyloidosis, are rare, but do arise in generalized dysreactive mesenchymal ("pararheumatic") disorders, in which a plasma cell reaction is the outstanding feature of the proliferative process.

These researches, the observation of a case clinically resembling rheumatoid arthritis but labelled by Chini as "dysprotidaemic joint lesions", and the finding of hyalinosis and paramylosis of the articular tissues, led to the belief that anomalous proteins or abnormal amounts of protein may accumulate in the joints with amyloid or paraamyloid local alterations.

The following case demonstrates the relation of joint disease with blood protein disorder.

Case History

A married woman, aged 47, had suffered from arthralgia at intervals since an operation 12 years before.

General History.—Her grandparents died in senility;

her father was alive and well, but suffered from sciatica; her mother, who died aged 62, had suffered from "joint disease". She was born at full-term, had regular onset of menarche, but slightly excessive and painful, was married at age 20 to a healthy man, and had had one healthy child, and no abortions.

At 34, after a partial surgical removal of ovary and uterus, the menses became scanty and delayed, and later (from December, 1952) menstruation had ceased completely. She had always worked as a housewife, lived in healthy surroundings, and had sufficient food.

Medical History.—As a child she suffered from rubella, and at 13 developed diffuse skin folliculitis, which disappeared at the menarche. At 19 she recovered from diphtheria without complications. At 23 she became very thin and suffered from psychoneurosis. Climato-therapy and general stimulants were of value. At 25, she complained of a pricking pain referred to the 7th, 8th, and 9th dorsal ribs, which was exacerbated by motion and refractory to ordinary antirheumatic treatment. As no vertebral lesion was seen radiologically, the patient received iodine for "a long period" and complete remission of symptoms occurred.

At 34, she noted that a vaginal discharge appeared and gradually increased; examination revealed uterine fibromyomatosis, and the patient thus underwent subtotal hysterectomy with hemianexiectomy.

Since then she has been suffering, especially during the winter, from arthralgia localized upon one or more joints; the pain disappeared with antirheumatic treatment.

About 18 months ago (at age 45) she had complained of an acute pain extending to the whole spine, especially the thoraco-lumbar tract; the tibiotarsal joints were sore and swollen, and their function impaired. Short febrile periods occurred, and urticaria-like rashes (itching, reddish pomphi) appeared sporadically on the chest and limbs. Meanwhile all the joints gradually became painful with alternate periods of exacerbation and quiescence. The disease was gradually developing into rheumatoid arthritis and when the patient was admitted to our clinic this diagnosis was confirmed.

Laboratory Findings.—Takata Ucko test highly positive (+++). Most colloidal lability tests positive. Sedimentation rate raised (Katz's index ranged between 80 and 100). No pathological data found in urinalysis and leucocyte counts. Blood picture normal.

Therapy.—After discharge from our clinic, the patient was given gold, hormones, vitamins, and liver-protecting drugs with some benefit.

Further Progress.—In November, 1953, she complained of an exacerbation of articular pains, with high intermittent fever, sharp and insistent cough, little sputum, dyspnoea, cyanosis, and low blood pressure; bluish patches (cutis marmorata), scattered on the whole surface of the limbs and chest, were intensified by the standing position and cold.

The patient was again admitted to the clinic on January 7, 1954.

Examination.—She was pale, thin, and anaemic-looking. Several bluish patches of vascular origin were

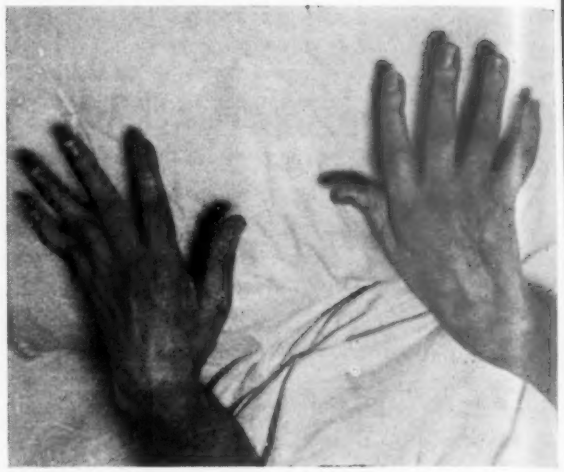


Fig. 1.—Patient's hands, showing distortion and swelling.

scattered on the skin of the limbs. The hands (Fig. 1) and the feet showed evident deformities and well-marked valgism. Articular motion was generally impaired. The nails were grooved and striped and bore signs of onychotrophy.

The chest expansion was slight, tactile fremitus and percussion resonance were impaired over both lung bases, the right base was raised and scarcely mobile, and the percussion note resonant through the rest of the field; diffuse rhonchi and moist rales were heard over both lungs, with coarse breathing and crepitant rales at the right base.

The cardiovascular system was normal. Blood pressure 120/90.

The tongue was dry, with reddened margins and central patches due to iodiomycosis, and the mouth and throat were red and covered with white patches.

The upper limits of the liver were slightly higher than normal, the lower edge being smooth, firm, and tender a hand's breadth below the costal margin. The spleen was soft and its inferior pole hardly felt during deep breathing.

Ankylosis and subluxation of the minor joints was present in both hands and feet. Slight tenderness and limitation of movement affected the remaining joints.

Laboratory Findings.

Urine: Specific gravity 1,010 to 1,015; acid reaction; albumin positive (+); sediment: few red blood cells, large number of leucocytes and epithelia; Bence-Jones protein revealed by subsequent analyses.

Blood: Haemoglobin 50 per cent., R.B.C. 3,400,000; haemoglobin index 0·70; W.B.C. 12,000.

Neutrophil leucocytes 73 per cent., eosinophil leucocytes 1 per cent., lymphocytes 25 per cent., monocytes 1 per cent.; mild aniso-poikilocytosis; platelets normal in shape and agglutination (ranging from 170,000 to 230,000/c. mm.).

Further blood examinations still showed a more or less marked anaemia due to treatment, and corresponding variations of the W.B.C. and differential counts. In spite of many careful and repeated observations only a few plasma-cells, or more often some Turk's cells and hyperbasophilic cells, were found.

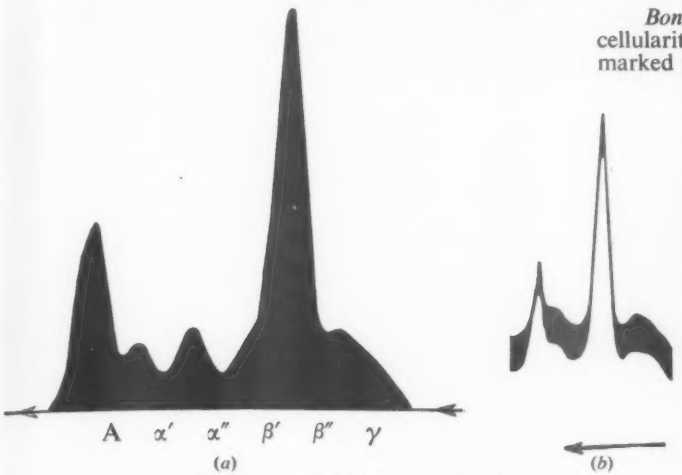


Fig. 2.—Electrophoresis (*a*) paper method; (*b*) Tiselius' method.

Erythrocyte Sedimentation Rate: First hour = 146 mm., second hour = 150 mm.; the first hour's value may be considered as Katz's index. Subsequent controls always confirmed a very high erythrocyte sedimentation rate with little variation, following the course of the disease and treatment. A greater reduction was obtained after ACTH administration.

Total Plasma Protein: From 7 to 8·5 g. per cent.

Takata Ucko Reactions: Strongly positive (++++); other tests based on plasma protein changes repeatedly positive.

Paper Electrophoresis (Fig. 2*a*): Total proteins 8·5 g. per cent.

Albumin 1·7 g. per cent.; globulin 6·8 g. per cent. (ratio 0·25); globulin 0·41 g. per cent.; α 0·75 g. per cent.; β 0·17 g. per cent.; β_2 4·1 g. per cent.; γ 1·37 g. per cent.

Electrophoresis (Tiselius) (Fig. 2*b*): Total proteins 8·5 g. per cent.

Albumin 1·73 g. per cent.; globulin 6·77 g. per cent. (A/G ratio 0·25); α globulin 0·71 g. per cent., β 4·97 g. per cent., γ 1·09 g. per cent.

Blood Chemistry:

Urea Nitrogen: 0·3 per thousand g.; further observations showed a rise to 1 g. per thousand, especially during the later stages;

Chlorine: 3·54 g. per thousand;

Chlorides: 5·84 g. per thousand;

Sugar: 1·15 g. per thousand;

Cholesterol: 292 mg. per cent., free 52 mg. per cent., esterized 240 mg. per cent.

Bone Marrow Examination (Fig. 3): Moderate cellularity, with some granuloblastic hyperplasia; marked plasmacytosis (0 to 10 per cent.) with morphological signs of "stimulation"; slight eosinophilia. L.E. phenomenon (incubation technique) absent.

A second sternal biopsy performed a month later furnished an abundant pinkish-grey material. At low magnification the smears appeared particularly hypercellular; at higher magnification the plasma cellular stem was the most prominent feature, as shown by the differential count (March 23, 1954):

Haemocytoblasts 0·2 per cent.; Myeloblasts 0·8 per cent.; Promyelocytes, neutrophil 0·4 per cent.; Myelocytes, neutrophil 2 per cent., eosinophil 0·4 per cent.; Metamyelocytes, neutrophil 3·4 per cent.; Band granulocytes, neutrophil 1·2 per cent.; Erythroblasts, basophils 0·04 per cent., polychromatophils 0·4 per cent., orthochromatophils 2 per cent.; Plasma cells 89 per cent.; Megakaryocytes 0·4 per cent.; Mitoses 0·4 per cent.

These figures show the striking rate of plasmacytosis; a systematic constant study of mitoses showed some unimportant abnormalities; no remarkable obstacle to maturation was noted.

A third bone-marrow puncture confirmed the previous data, though a slight decrease of plasmacytosis was observed. This bone-marrow count was obtained on March 30, 1954, after a course of phenylbutazone.

Haemocytoblasts 1·2 per cent.; Myeloblasts 1·4 per cent.; Promyelocytes, neutrophils 2·2 per cent.; Myelocytes, neutrophils 6·0 per cent., eosinophils 0·6 per cent.; Metamyelocytes, neutrophils 14·0 per cent., eosinophils 1·2 per cent.; Staff granulocytes, neutrophils 13·0 per cent.; Proerythroblasts 0·2 per cent.; Erythroblasts, basophils 2·4 per cent., polychromatophils 4·0 per cent., orthochromatophils 4·0 per cent.; Plasma cells 47·6 per cent.; Endothelial cells 1·2 per cent.; Megakaryocytes 0·2 per cent.; Mitoses 0·4 per cent.

Coagulation Test: Tourniquet, hammer, and pinch

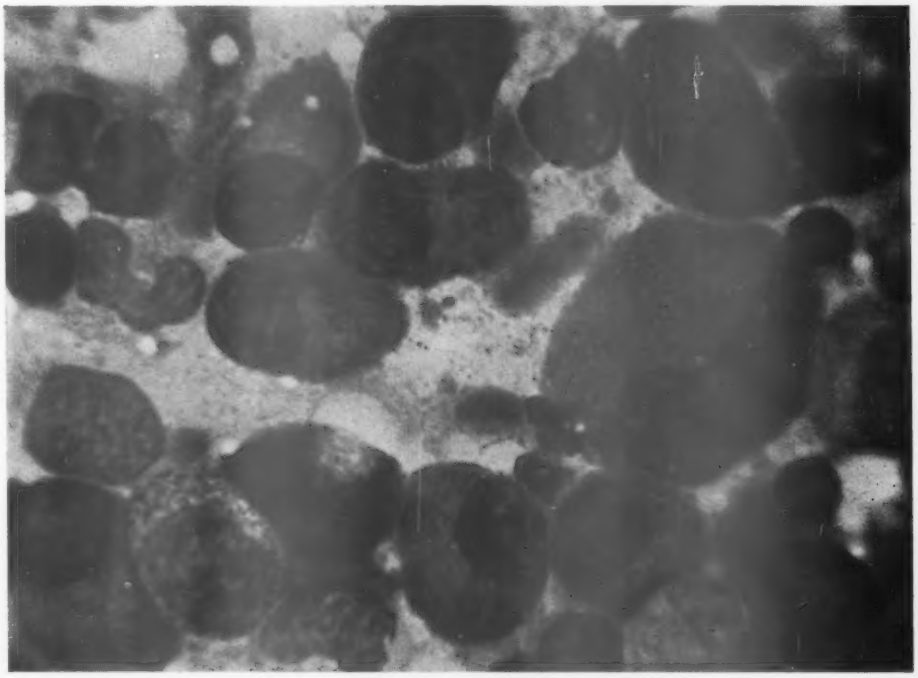


Fig. 3.—Bone-marrow.

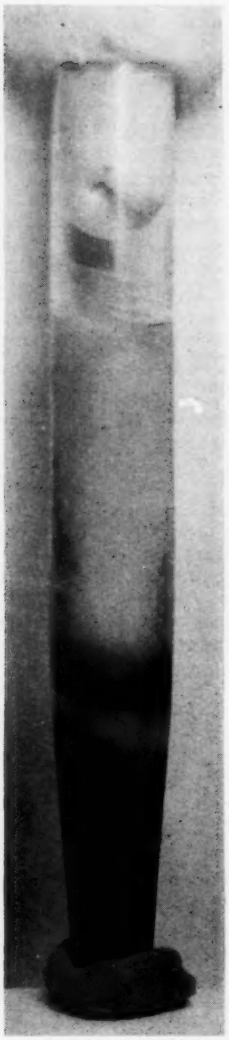


Fig. 4.—Blood coagulation test.

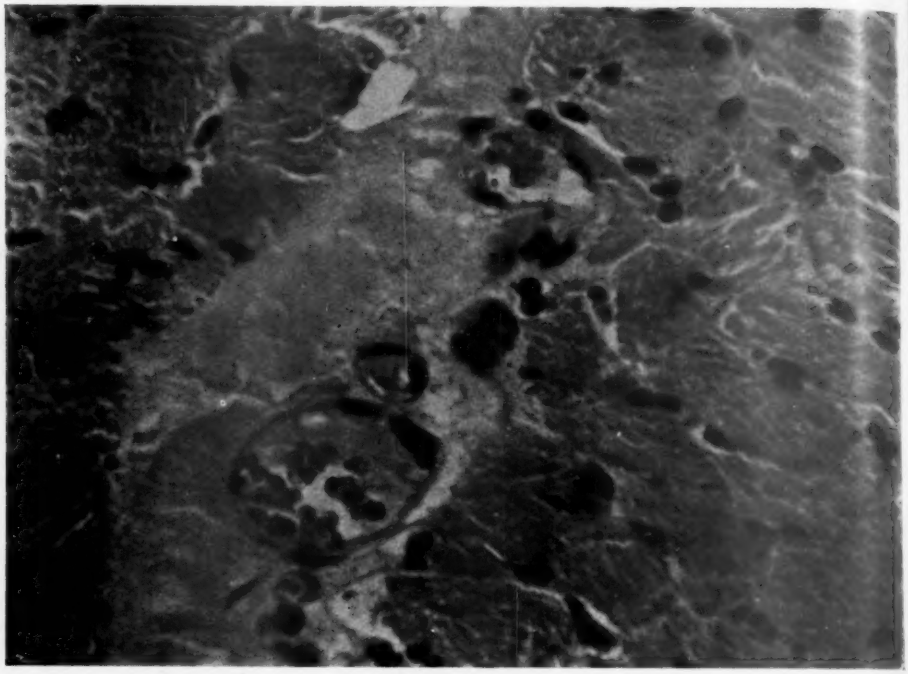


Fig. 5.—Muscle biopsy from the upper arm.

tests, slightly positive; bleeding time moderately delayed (4½ min.); in testing clotting time and clot-retraction time, a prompt and massive coagulation with clouding and whitening of the upper part occurred (Fig. 4).

The amount of serum necessary for examinations could be obtained only by immediate incubation of the blood sample at 37° C. The serum specimens (fluid when kept at thermostat temperature) appeared much thicker when stored at room temperature in a refrigerator.

Quick's time 20 sec. prothrombin activity 33 per cent. of normal;
Recalcification time 3 min. 50 sec.;
Residual prothrombin after 60 min. 21 per cent.;
Accelerating power of serum (prothrombin conversion and S.P.C.A. formation (Meneghini and Felini, 1954) showed slow and defective thrombin formation and lack of S.P.C.A.

Blood Culture on several media was negative; Wright and Vidal reactions negative; Wassermann reaction and other tests for syphilis negative; *Mycobacterium tuberculosis* negative.

Cerebrospinal Fluid (lumbar puncture): Clear as water, containing 3 cells c.mm., albumin 0·2 g. per thousand, sugar 0·65 g. per thousand; Wassermann reaction negative; Nonne Appelt negative; Pandy and Weichbrodt reaction showed slight opalescence.

Heart: An electrocardiogram (January 9, 1954) showed only sinus tachycardia with ventricular extrasystole. Another test (January 21, 1954) showed a partial atrioventricular block with nodal escape beats and bradycardia. By February 12, 1954, the block had disappeared.

Muscle Biopsy (Fig. 5) from the biceps brachii: Diffuse sclerohyalinosis; lymphocytes and plasma cells infiltrating the interstices and forming dense perivascular muffs around the undamaged arterial walls.

Synovial Biopsy from the knee-joint: Cells with plasmacellular characteristics (eccentric nuclei, basophilic cytoplasma, perinuclear halo) scattered or gathered between coarse strands of connective tissue, the blood vessels being surrounded by lymphocyte-like cells. Slight infiltration formed by plasmacytomatous elements.

Ocular Examination (carried out by Dr. Cucco at the Ophthalmological Clinic): Signs of healed iridocyclitis were found in both eyes. Slightly opaque patches on the corneae, made ocular examination very difficult.

X-ray Examinations

Skull: Normal.

Spine: Low grade, leftward scoliosis of superior dorsal segment, with no structural changes, some degree of decalcification and osteoporosis in the terminal lumbar tract (Fig. 6, opposite). Pseudo-cystic appearances, due to lacunar porosis, on the edges of L4 and L5. Posterior arches of sacro-iliac synchondroses showed inter-articular defects.

Legs: Small spindle-shaped lacunae at both ends of the tibiae and fibulae and at the distal end of the femur.

Hands and Wrists: Atrophy of the carpus and metacarpus, and of the epiphysis of the forearm (Fig. 7, opposite).

Thorax: A series of radiographs in January and February, 1954 (Figs 8*a*, *b*, *c*, opposite) followed the capricious development of pulmonary damage. The

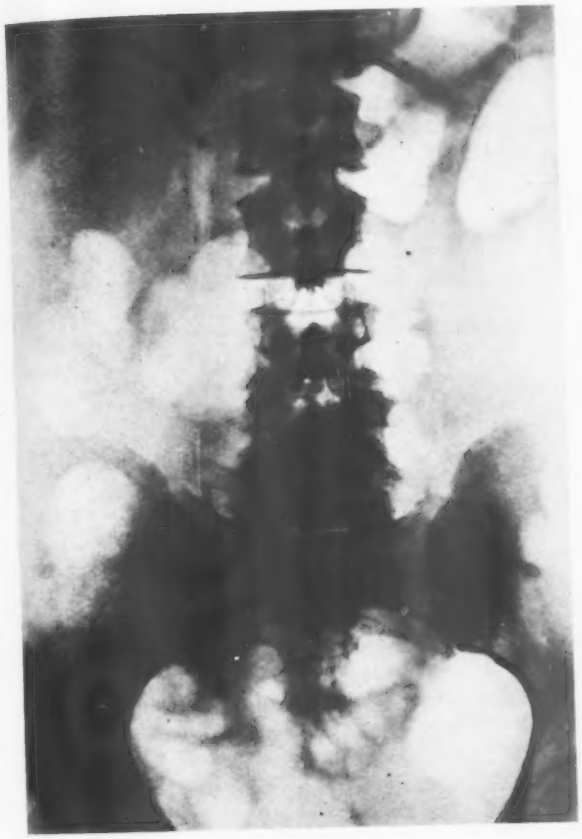
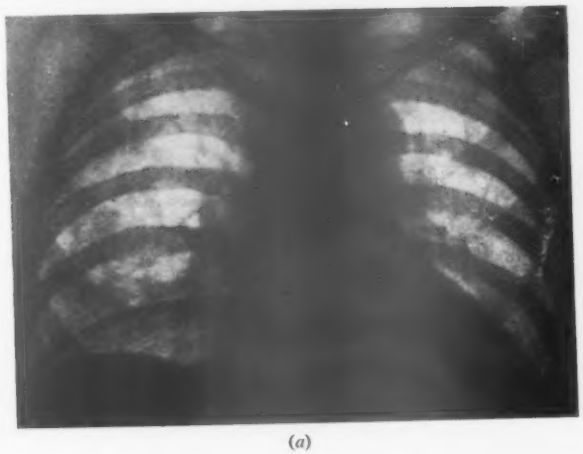


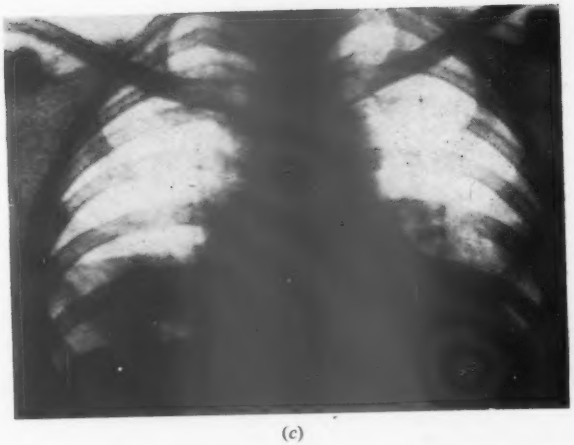
Fig. 6.—Spinal *x* ray.

Fig. 7.—*X* ray of hands and wrists.



(*a*)

(*b*)



(*c*)

Fig. 8.—Thorax *x* rays, showing development of pulmonary damage.
(*a*) 14.1.54
(*b*) 21.1.54
(*c*) 12.2.54

most important findings were always seen in the right field, where wide hypodiaphanic areas were present. Combined treatment with ACTH and antibiotics caused both pulmonary fields to clear up completely.

Clinical Course.—On admission to hospital, clinical signs of bilateral pulmonary involvement and high fever (38-39° C.) were present. For this reason, and also because of collapse and poor general condition, penicillin 800,000 I.U. daily, streptomycin 1 g. daily, and cardiotonic and detoxicating treatment was given, but no improvement resulted.

On January 22, 1954, the patient vomited a yellow-greenish, bitter fluid; she showed anorexia, toxicosis, severe collapse, and oropharyngeal mucous inflammation, with diffuse moniliasis.

Pre-coma followed, with impaired and sterterous respiration, increased pulmonary involvement, weak rapid pulse, blood pressure 70-80 mm. Hg, and temperature 35·6° C.

Antibiotics were then withdrawn and the patient received only cardiotonic and detoxicating treatment.

After 2 days the heart block disappeared and the electrocardiographical tracing was practically normal, but the fever increased. Because of some migrating bronchopulmonary areas the patient was given terramycin (250 mg. daily) by drip phleboclysis, and ACTH intramuscularly. The temperature responded well within 3 days and was kept at normal levels.

Electrophoresis and bone-marrow examination now enabled a clear diagnosis to be made.

After ACTH and terramycin had been given both pulmonary fields cleared and a slight fall was seen in the erythrocyte sedimentation rate.

The high doses of ACTH were discontinued, and streptomycin administration was started, owing to a small effusion in the right pleura, which was found by an explorative puncture; a thick, yellowish, clear fluid was extracted and coagulated immediately; the Rivalta reaction was strongly positive.

The patient's general condition improved slightly, moniliasis disappeared, and feeding was again possible.

Twenty days after withdrawal of streptomycin, a new slight febrile attack occurred, with swelling, reddening, and pain in the finger joints.

Phenylbutazone (1 g. daily for one week) caused improvement of these symptoms, but the patient died in May, 1954.

Discussion

Since clinical and radiological features of rheumatoid arthritis were present in our case, the diagnosis of rheumatoid arthritis secondary to myeloma could not be rejected. A few similar cases, considered by Chini (1955) to be cases of "myelomatous dysprotidaemic arthropathy", have already been reported in the literature.

In this instance our attention was first drawn to the rheumatoid arthritis and afterwards to the plasmacytoma. The following features supported the first diagnosis:

(*a*) articular pattern, with an acute onset, followed by chronic progression. Through many exacerbations, the joint involvement grew gradually worse, and finally presented the classical picture of rheumatoid arthritis;
(*b*) constantly raised erythrocyte sedimentation rate;
(*c*) striking dysprotidaemia with inversion of A/G ratio and increase of the β globulin fraction;
(*d*) mild changes in the peripheral blood (mononuclear cells showed a degree of hyperbasophilia); conversely, plasma-cells were present in the bone marrow at the rate of 8 to 10 per cent., within the highest limits associated with rheumatoid arthritis;
(*e*) slight enlargement of the spleen;
(*f*) iridocyclitis accompanied by the so-called "dysprotidaemic fundus" picture;
(*g*) occasional Bence-Jones proteinuria, evident in the terminal stages;
(*h*) moderate osteolytic lesions peculiar to rheumatoid arthritis;
(*i*) vascular changes (cutis marmorata) which may be considered among the capillary phenomena secondary to rheumatoid arthritis, and may even induce acropurpura (Anderson and Samuelson, 1944).

To justify the second diagnosis, differential criteria rather qualitative than quantitative are required:

(*a*) sedimentation rate abnormally raised;
(*b*) blood plasma disorders and related phenomena extremely serious, the β globulin peak being the main feature in the electrophoretic curve;
(*c*) bone-marrow plasmocytosis, moderate in the early stages, and later reaching a very high level;
(*d*) lung involvement typical of myeloma;
(*e*) bone changes secondary to myeloma, though of limited extent;
(*f*) Bence-Jones proteinuria;
(*g*) kidney impairment (shown by the high degree of albuminuria and blood nitrogen) suggestive of a renal disorder.

The type of arthropathy seen in this case is one that may be encountered in myeloma.

The diagnosis of atypical myeloma-like rheumatoid arthritis or of rheumatoid arthritis turned to myeloma would be hazardous on the basis of the laboratory findings, but the development of myeloma on a biological background already greatly modified by rheumatoid arthritis is a possibility. The relationship between the two diseases depends first on the association of rheumatoid arthritis with myeloma, and secondly on joint involvement typical of early myeloma; the dysprotidaemic pathogenesis of this disease was recently formulated by Chini, who suggested the description "dysprotidaemic joint disease".

Laboratory findings, and, in our case, radiological findings also, place rheumatoid arthritis close to myeloma, the differences being rather quantitative than qualitative. One might, therefore, expect a frequent clinical association of the two conditions, whereas, in fact, this is rare. However, the syndrome, having once been described, may be more frequently noted in the future, especially in cases of rheumatoid arthritis characterized by a severe and lethal progress in which serious plasma disorders rapidly affect the general health.

The practical interest of the case reported above lies in the differential diagnosis of some articular lesions commonly believed to be peculiar to rheumatoid arthritis. Many other "rheumatoid" joint alterations are known to occur in the so-called "pararheumatic" diseases (Friedman, Schwartz, Trubek, and Steinbrocker, 1953), in the Pierre-Marie syndrome, and in the so-called "dystrophic rheumatisms". The possibility of dysprotidaemic arthropathies of the rheumatic type has also to be kept in mind.

Furthermore, the present case offers an approach to the problem of inter-relations between protein disorders and the chronic articular ailments which may be directly correlated with them.

Summary

A case of polyarthritis is described, in which the clinical appearances had led to an early diagnosis of rheumatoid arthritis; subsequently, the clinical course and laboratory findings suggested plasmacytomatosis. A diagnosis of plasmacytoma accompanied by dysprotidaemic joint disease seems the more probable. This assumption is based on both the clinical course (atypical pulmonary involvement, severe and fatal progress) and the laboratory findings (tests for dysprotidaemia and bone-marrow function, muscular and synovial biopsies, and *x*-ray examinations).

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Arthrite rhumatismale et plasmocytomatose

RÉSUMÉ

On décrit un cas de polyarthrite chronique dont le tableau clinique fit d'abord penser à l'arthrite rhumatismale; plus tard l'évolution clinique et les résultats de laboratoire suggérèrent la plasmocytomatose. Le diagnostic de plasmocytoma accompagné de maladie articulaire dysprotidémique semble plus probable. Cette hypothèse se base aussi bien sur l'évolution clinique (implication pulmonaire atypique, évolution grave vers la mort) que sur les résultats de laboratoire (tests de dysprotidémie, ponction de la moelle osseuse, biopsies musculaires et synoviales et examens radiologiques).

Artritis reumatoide y plasmocitomatosis

SUMARIO

Se describe un caso de poliartritis crónica con un cuadro clínico que al principio llevó al diagnóstico de de artritis reumatoide pero que luego, en vista de la evolución clínica y de los resultados de laboratorio, hizo pensar en la plasmocitomatosis. El diagnóstico de plasmocitoma acompañado de enfermedad articular disprotidémica parece más probable. Esta hipótesis se basa tanto sobre la evolución clínica (compromiso pulmonar atípico, evolución grave hacia la muerte) como sobre los resultados de laboratorio (disprotidemia, punción de la médula ósea, biopsias musculares y sinoviales e investigación radiológica).

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PARAFFIN-WAX BATHS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

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The physical treatment most frequently used for the hands in rheumatoid arthritis is the local paraffin-wax bath. It was first described by Humphris (1919) and since then has been in general use. The standard textbooks of physical medicine and rheumatology refer to wax baths as being of value, but we have been unable to find any critical attempt to assess this. It is unusual for a patient with rheumatoid arthritis to be admitted to this hospital who has not received prolonged courses of paraffin-wax baths at other hospitals, usually in the out-patient department. Wax baths are also extensively used at the Devonshire Royal Hospital, approximately 10,000 individual wax treatments being given each year.

Although evaluating the effect of any form of therapy in rheumatoid arthritis is notoriously difficult, especially if dramatic results cannot be expected, it was decided to investigate the progress of the hands treated with paraffin wax, and compare them with those of an untreated series of patients.

Method

Ninety successive in-patients with rheumatoid arthritis referred to the physiotherapy department for paraffin-wax hand baths were divided into three groups, the choice being made at random by the department clerk. Group I received no local treatment to the hands, Group II had wax baths daily for 3 weeks, and Group III had wax baths daily for 6 weeks. The patients were unselected, except that subjects who had recently taken, or were taking, cortisone or ACTH were excluded from the investigation.

All patients were taking calcium aspirin gr. 10-15 three times a day during their trial period. They received no other local treatment to the hands during the trial period, but they were all carrying out a general programme of physical rehabilitation linked with the activity of their disease.

The method of applying the wax was by the patient dipping both hands into the bath of melted wax (at 110°-115° F.) six times, so forming a glove of wax. The hands were then wrapped in a layer of greaseproof paper, and two towels, which were retained for 20 minutes. After this, supervised finger exercises were performed. Group I patients did no finger exercises, and Group II subjects discontinued them after the third week.

Skin temperature measurements, using the Cambridge skin thermometer, were taken of the pulp of the middle finger and the skin of the dorsum of the third metacarpal head in six subjects, before, immediately on withdrawing the hands from the wax baths, and at 10-minute intervals for a further 60 minutes.

When the hands were withdrawn from the wax bath the thermocouples were inserted under the wax into contact with the hand, and cooling curves plotted. The rise in temperature was similar in the same hand at both sites. The range of temperature rise was from 2·9-9·5° C. (mean 5·8°). Skin temperature rapidly fell to initial values or below within a time range of 10-60 min. (mean 37). It is clear that with the technique employed a fair rise of temperature is obtained, but is not long maintained.

Assessment

The hands were examined by a team of assessors, one of them (J.B.M.) being present on every occasion. The subjects were initially examined on 2 successive days before admission to the treatment scheme, and the mean of these readings used to give an initial base line. They were further examined weekly for 6 weeks. All assessments of the same patient were carried out on the same day of the week and at the same time of day. A special proforma was used. The duration of disease, stage and functional grade of the disease (Steinbrocker and others, 1949), erythrocyte sedimentation rate (Westergren), local deformity of the hands, and general treatment were noted. The local assessment was comprehensive, including examination of every joint in the hand. The distal phalanges of all the fingers were considered as a single joint for record purposes, as was the wrist joint.

The following data were recorded serially for each joint of the hand:

(1) *Tenderness*
- (*a*) Clinical impression, by finger pressure, graded 0-3 in order of increasing severity.
- (*b*) Pressure pain, with an algesiometer, recorded in lb. (Janus, 1950).

(2) *Pain*, graded 0-3 in order of increasing severity
- (*a*) at rest;
- (*b*) on movement.

(3) *Swelling*
- (*a*) Clinical impression, graded 0-3 in order of increasing severity.
- (*b*) Circumference of proximal interphalangeal joints, measured by ring sizes.

Total hand function was measured separately for each hand by the following tests:

(1) *Grip*
- (*a*) Clinical impression by hand grip, graded 0-3 (0 = normal, 1 fair, 2 poor, 3 absent).
- (*b*) Rubber bag ergometer; sustained height in mm. Hg.

(2) *Dexterity*
- (*a*) Number of beads picked up and placed in a standard container in 30 sec.
- (*b*) Distance thread of a standard screw could be turned in 15 sec.

At the third and sixth weeks the assessment team, using all the collected data, arrived at an overall impression of the patients' progress both in general condition and in the hands. At the sixth week the patients also recorded their own total impression of their hands. These were recorded as:

−1 = worse;
0 = no change;
1 = slight gain;
2 = moderate gain;
3 = major gain.

During their trial period nineteen of the subjects left the series owing to discharge from hospital or other reasons; three of the 19 had developed wax rashes. A total of 71 subjects completed the full 6 weeks' observation period. The withdrawals affected the size of the groups about equally, and Table I shows that it is unlikely that they would have altered the final results in any way.

Results

The three groups were roughly matched in numbers, age distribution, stage of disease, and general progress. The relevant data is incorporated in Table II, which also includes alterations in the erythrocyte sedimentation rate. These are graded −1 to 3:

−1 = increased;
0 = no change;
1 = decrease of less than 20 mm.;
2 = decrease 20-40 mm.;
3 = 40 mm. or more.

In no subject did the erythrocyte sedimentation rate return to normal.

TABLE I
PARTICULARS OF NINETEEN WITHDRAWALS

Group	No. of Subjects	Sex		Mean Age (yrs)	Mean Duration of Disease (yrs)	Disease								Assessment at 3 weeks						Week of Withdrawal					
						Stage				Grade															
		M.	F.			1	2	3	4	1	2	3	4	−1	0	1	2	3	—	0	1	2	3	4	5
I	7	1	6	49	2½	5	2	—	—	2	5	—	—	—	2	2	2	—	1	—	1	—	4	2	—
II	5	1	4	44	4½	4	0	1	—	1	4	—	—	—	1	3	1	—	—	0	0	0	2	2	1
III	7	2	5	51	4	4	2	1	—	0	6	1	—	—	1	2	2	—	2	—	2	0	1	2	2

TABLE II
DETAILS OF THREE GROUPS INVESTIGATED

Group	Total No. of Subjects	Sex		Mean Age (yrs)	Mean Duration of Disease (yrs)	Disease								General Progress					Change in Erythrocyte Sedimentation Rate*					E.S.R. (Westergren) (mm./hr)	
						Stage				Grade															
		M.	F.			1	2	3	4	1	2	3	4	−1	0	1	2	3	−1	0	1	2	3	Initial	Final
I	23	4	19	46	7	11	8	4	—	6	16	1	—	3	8	12	—	—	6	5	11	—	—	46	42
II	25	9	16	50	7·4	8	11	6	—	2	21	2	—	4	4	17	—	—	9	4	10	—	—	44	46
III	23	4	19	48	8·5	5	11	7	—	2	16	5	—	3	7	13	—	—	6	4	9	—	—	50	52

* E.S.R. series incomplete.

The results of the individual methods of assessment do not appear to be worth reporting in full detail. In many the alterations observed week by week were so small that no useful information could be recorded (*e.g.* joint deformity). Quite commonly a change in one joint would be accompanied by a change in the opposite direction in another joint of the same hand, so that the composite picture appeared unchanged.

As wax baths are usually considered to relieve pain and tenderness and reduce swelling (Kovács, 1945), the results obtained with some tests for these are reported. The strength of grip is frequently used in assessing progress in rheumatoid arthritis and these results are also included.

The figures for "pain" were reached by adding the numerical grade (0-3) of pain on movement for each joint of the hand, giving a composite figure for each hand at each particular examination. The average of both hands was recorded, and the mean weekly values of these figures, as found for each of the three groups, are given in Table III.

Values of "tenderness" were similarly recorded. The size of ring fitting each proximal interphalangeal joint was added, and the average value of each pair of hands gave a composite figure. The mean value was recorded weekly for each group.

Strength of grip (in mm. Hg) and "dexterity" (number of beads picked up in the standard time) were measured for each pair of hands, the average figure being recorded. The weekly group mean values are given in Table III.

The final column in Table III shows the numerical difference between the initial and final mean values for each particular test, and is thus a measure of progress made in the 6 weeks.

Table III indicates that initially Group I was a less severely affected group than the others. At the end of 3 weeks all three groups had made similar subjective and objective progress, the difference between actual "scores" reflecting their initial values. At 6 weeks our more objective tests (swelling, grip, dexterity) show very similar progress in all groups, and so do the subjective tests for Groups I and III. However, in comparison, Group II has made little progress and appears to have deteriorated sharply between the fifth and sixth weeks.

These results as a whole fail to show that our subjects gained any benefit from their course of wax baths.

Table IV (opposite) shows the overall assessments at 3 and 6 weeks respectively: At 3 weeks the three groups are almost identical; at 6 weeks the groups are again similar, although Group II is slightly the worse, and Group III slightly the best of the three.

By 3 weeks more than 50 per cent. of the patients had improved a little, and the improvement was rather more pronounced in the wax-treated groups. By the sixth week there was a further improvement, mainly in Groups I and III, and in these 65 and 73·8 per cent. respectively showed improvement. In Group III no patients were worse than before treatment, and 30·4 per cent. had made "a moderate

TABLE III
MEAN WEEKLY VALUES OF TESTS FOR PAIN, TENDERNESS, SWELLING, GRIP, AND DEXTERITY

Test	Week		0	1	2	3	4	5	6	Total Change
Pain	Group	I	1·2	1·0	1·1	0·4	0·4	0·3	0·3	0·86
		II	1·9	1·5	1·1	1·2	1·3	1·3	1·6	0·28
		III	1·8	1·7	1·3	1·0	1·0	1·3	0·9	0·87
Tenderness ..	Group	I	8·9	8·2	8·0	7·1	6·1	6·6	5·8	3·1
		II	11·0	11·4	8·9	9·0	10·5	9·0	10·4	0·6
		III	11·9	10·6	10·6	9·4	8·7	8·7	7·2	4·7
Swelling	Group	I	3·5	3·4	3·3	3·2	3·3	3·4	3·3	0·22
		II	4·8	4·8	4·8	4·7	4·8	4·8	4·7	0·16
		III	4·1	4·1	4·0	4·1	3·9	3·9	3·9	0·15
Grip	Group	I	110	119	118	121	127	121	128	18
		II	105	119	124	116	118	120	116	11
		III	79	79	86	84	93	89	91	12
Dexterity	Group	I	31	34	33	34	34	34	35	4
		II	28	30	32	31	32	32	33	5
		III	26	29	31	29	30	31	31	5

TABLE IV
OBJECTIVE ASSESSMENT OF IMPROVEMENT AT 3 AND 6 WEEKS

Group		I	II	III	I	II	III
Grade	−1	4·4	4	8·7	4·4	12	—
	0	47·8	40	30·4	30·4	32	26·2
	1	43·4	52	52·2	47·8	44	43·4
	2	4·4	4	8·7	17·4	8	30·4
	3	—	—	—	—	4	—
Time (wks)		3			6		

gain". Only one subject in the whole experiment achieved a major gain, and this was in Group II.

The patients' impressions of their own progress at 6 weeks are shown in Table V. They closely approximate to those of the assessors, and are, in fact, identical for the untreated series.

TABLE V
PATIENTS' SUBJECTIVE EXPERIENCE OF IMPROVEMENT

Group		I	II	III
Grade	−1	4·4	12	4·4
	0	30·4	20	13·0
	1	47·8	60	47·8
	2	17·4	8	34·8
	3	—	—	—
Time (wks)		6		

Only thirteen out of the 71 subjects in the trial achieved a Class II overall improvement (a moderate gain). One of these was assessed as a major gain. four of these were in the untreated series, two in the partly treated, and seven in the fully treated group. The details of these thirteen subjects are set out in Table VI. It will be seen that there are apparently no common factors. They were of a wide age group (12-71 yrs, mean 50·5). There was a rather high proportion of early cases, six of the subjects being at Stage I of the disease (nearly 50 per cent.) as compared with 34 per cent. in the whole series. Only three subjects had a duration of disease exceeding 5 yrs (mean 4·9), as opposed to 7·6 yrs in the whole series. Pain, tenderness, weakness of grip, and swelling were not marked features in these subjects as a whole, but varied widely from case to case. The most noteworthy fact is that all derived considerable relief from pain, and twelve of the thirteen became completely pain-free, although tenderness remained, usually at a reduced level. Despite this, objective tests sometimes showed a poorer performance. These findings were no more marked in the treated than in the untreated subjects.

Discussion

Although the number of subjects studied in this investigation is small for analysis, they have been followed in detail. The changes occurring in the three groups were almost identical for the first 3 weeks of the test. After 6 weeks there was still little comparative difference in the local condition of the hands in the treated and control group; in fact the subjects who had the 3 weeks' course of treatment deteriorated and were subjectively worse in the end than the untreated patients. Such relief as did occur after the wax baths was of short duration, and the rapid return of skin temperature to its initial level also indicates that only temporary effects are produced.

Table III shows that a considerable improvement of pain in the hands can be expected from 6 weeks' institutional treatment, without any local therapy. Claims that any method of treatment produces improvement must take this into consideration.

TABLE VI
DETAILED PARTICULARS OF THIRTEEN PATIENTS WHO SHOWED IMPROVEMENT (AVERAGE OF THE TWO HANDS)

Group	Case No.	Age (yrs)	Sex	Duration of Disease	Disease		Tenderness		Grip		Pain		Swelling		Dexterity		Erythrocyte Sedimentation Rate (Westergren) (initial) (mm./hr)	Result
					Stage	Grade	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final		
I	28	56	F	3	3	2	15	5	70	35	1	0	4	4	25	27	93	2
	43	60	M	2	2	2	10	2	100	175	0	0	10	8	31	39	60	2
	54	53	F	10	2	2	20	11	61	53	3	0	3	3	27	33	28	2
	83	39	F	1	1	2	5	2	85	112	0	0	6	4	22	28	14	2
II	8	57	M	5	1	2	11	0	222	235	3	0	7	7	28	34	45	3
	84	62	M	1	1	2	14	1	250	238	0	0	5	5	28	32	25	2
III	3	71	F	1	2	2	4	4	75	70	2	0	1	1	17	22	50	2
	15	12	F	1	1	2	10	0	43	73	0	0	0	0	31	39	40	2
	18	23	F	1	1	2	8	2	40	70	1	0	0	0	25	32	70	2
	24	64	F	4	1	2	19	10	66	88	2	0	6	5	25	39	62	2
	85	44	F	19	3	2	25	18	38	50	9	3	5	4	13	18	27	2
	88	54	F	5	2	2	12	8	80	90	1	0	6	6	30	30	80	2
	91	65	F	11	3	3	16	7	50	85	1	0	2	2	24	37	50	2

The close similarity between the patients' subjective impression of progress and that made by an observer using all the data obtained in a comprehensive assessment throws doubt on the value of the so-called objective tests in rheumatoid arthritis. Relying on a single "objective" or "subjective" test may be especially misleading. In all these tests the assessor must depend on the patients' co-operation, and this introduces a high "subjective" element (Harris, 1950).

Mandel (1954) compared objective and clinical assessments of progress with the patients' general impression, and reached the conclusion that the patients' impression is as satisfactory as the most objective of assessment techniques. This accords with our findings.

Coyer (1954) used citrate iontophoresis in fifteen subjects with rheumatoid arthritis, and has compared their progress with that of twenty similar subjects given galvanic hand baths. In the control group eighteen subjects had little or no relief, and strength of grip showed only a small increase.

In the citrate ionization group, thirteen of the fifteen claimed marked relief of pain and stiffness of the joints, lasting for 4-5 hrs after treatment. Grip strength improved markedly, with an average rise of over 100 mm. Hg on the ergometer. This compares with an average rise of 12 mm. Hg in our 6-week wax series.

The technique of wax baths used in this investigation has been practised in this hospital for at least 15 years and is widely used elsewhere. Paraffin-wax when first introduced was used as a continuous immersion bath, lasting between 20 and 30 minutes. The change in technique from baths to packs was probably due to the increased number of patients who can be treated in the same bath by dipping and packing, as compared with continuous immersion. An investigation of the use of this latter technique in treating the rheumatoid hand would appear to be necessary before discarding paraffin-wax baths.

Summary

(1) A comparative study of the progress of the hands in rheumatoid arthritis has been made in three groups of subjects:

(*a*) No local treatment of the hands (23 subjects).
(*b*) Paraffin-wax baths and packs, five times a week for 3 weeks (25 subjects).
(*c*) Paraffin-wax baths and packs, five times a week for 6 weeks (23 subjects).

(2) A comprehensive assessment was carried out initially and weekly in each group for 6 weeks.

(3) No difference was found between the three groups at 3 weeks, but at 6 weeks the group treated continuously with wax was slightly better.

(4) A study of patients who did improve did not indicate any method of selecting patients most likely to benefit from wax-bath treatment.

(5) Paraffin-wax hand baths are of little value in the treatment of rheumatoid arthritis.

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Bains de paraffine dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

(1) On a étudié le progrès comparatif des mains dans l'arthrite rhumatismale dans trois groupes de sujets:

(*a*) Pas de traitement local des mains (25 sujets).
(*b*) Bain et enveloppement de paraffine, cinq fois par semaine pendant 3 semaines (25 sujets).
(*c*) Bain et enveloppement de paraffine, cinq fois par semaine pendant 6 semaines (25 sujets).

(2) On effectuait une évaluation compréhensive, initiale et hebdomadaire pendant 6 semaines dans tous les groupes.

(3) On n'a pas trouvé de différence entre les trois groupes au bout de trois semaines, mais au bout de six semaines le groupe traité continuellement par la paraffine se trouvait un peu mieux que les deux autres.

(4) L'étude des ceux qui n'accusaient pas d'amélioration n'a indiqué aucune méthode qui permette de choisir des malades susceptibles de tirer avantage du traitement par des bains de paraffine.

(5) On a conclu que les bains des mains dans la paraffine sont peu utiles comme traitement de l'arthrite rhumatismale.

Baños de parafina en el tratamiento de la artritis reumatoide

SUMARIO

(1) Se procedió a un estudio comparado del progreso de las manos en la artritis reumatoide en tres grupos de sujetos:

(*a*) Sin tratamiento local alguno de las manos (25 sujetos).
(*b*) Baños y envoltura de parafina, cinco veces por semana durante 3 semanas (25 sujetos).
(*c*) Baños y envoltura de parafina, cinco veces por semana durante 6 semanas (25 sujetos).

(2) Se hizo una avaluación comprensiva, inicial y semanal, durante 6 semanas en todos los grupos.

(3) No se observó diferencia entre los tres grupos al cabo de tres semanas, pero al cabo de seis semanas el grupo tratado continuamente con parafina encontrose algo mejor que los demás.

(4) El estudio de los que no acusaron mejoría no dió indicación alguna que permitiera la selección de los enfermos susceptibles de beneficiar del tratamiento con baños de parafina.

(5) Se concluyó que los baños de manos en parafina no son muy útiles en el tratamiento de la artritis reumatoide.

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SERIAL STUDIES OF SYNOVIAL FLUID IN EVALUATING INTRA-ARTICULAR AGENTS

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One of the most difficult problems in the study of rheumatic diseases is the evaluation of an anti-inflammatory response. That this is true in intra-articular as well as systemic therapy is illustrated by the divergence of results reported in the literature. For example, Cohen and others (1954) concluded, by purely clinical evaluation in a large number of patients, that cortisone acetate was equally as effective as hydrocortisone acetate, while studies based on more objective criteria by Duff and others (1951), Hollander and others (1951), Stevenson and others (1952), Ziff and others (1952), and Kersley and Desmarais (1952) clearly demonstrated its relative ineffectiveness.

The present study poses two questions:

(1) What are the changes in the synovial fluid examined by the usual techniques after the intra-articular administration of an agent of known effectiveness—hydrocortisone acetate?

(2) Will serial analyses of synovial fluid permit evaluation in a limited number of patients of an agent of unknown effectiveness—hydrocortisone?

The latter preparation differs from hydrocortisone acetate in its increased solubility in synovial fluid (Macek and others, 1952), and is, therefore, of considerable theoretical interest.

Method

108 knee-joint aspirations were performed on ten patients with active rheumatoid arthritis with effusions of the knee, bilateral in two. The patients ranged from 29 to 69 years of age and the duration of disease from 2 months to 36 years. The patients were fasting at the time of each procedure. The puncture site was infiltrated with 1 per cent. procaine. After one or two control aspirations, 1 ml. of a steroid suspension (50 mg./ml.) was administered intra-articularly to each patient. Serial aspirations, removing all available fluid, were then performed on approximately the second, fourth, and sixth day, and later, if necessary, until the characteristics of the fluid had returned to their original pattern. The patients were then given the next test substance and the response was followed in a similar manner. Nine of the patients received hydrocortisone acetate (50 mg./ml.), ten hydrocortisone (50 mg./ml.), three a placebo containing 50 mg. cholesterol, and three a saline placebo. The suspending media in each instance was identical and consisted of physiological salt solution containing 4 mg. Polysorbate 80, and 5 mg./ml. carboxymethylcellulose, preserved with 0·9 per cent. benzyl alcohol. The order of administration of the drugs was varied from patient to patient, and in a number of instances the same preparation was administered successively to the same patient. Because it was soon observed that the synovial fluid alterations were of much longer duration after the instillation of hydrocortisone acetate this steroid was usually the last to be evaluated.

Each synovial fluid sample was analysed by the techniques customarily used in this clinic (Ropes and Bauer, 1953). These included:

Volume of fluid available by aspiration;
White blood cell count with saline diluent;
Differential cell count;
Nature of mucin precipitate obtained in 1 per cent. acetic acid (Ropes and Bauer, 1953);
Viscosity determined by Hess viscosimeter;
Blood and synovial fluid sugar by "macro" method (Folin and Wu, 1920; Folin, 1929).

Not all determinations were performed on each aspirate because occasionally the volume of fluid obtained was inadequate.

Results

A comparison of the effect of hydrocortisone and hydrocortisone acetate injected intra-articularly is summarized in the Table (overleaf).

The extent of symptomatic relief was based on the patient's own evaluation of the agents. Care was taken not to inform the patients whether a given aspiration was merely for study or whether a steroid or placebo was being administered. The greater incidence and degree of symptomatic relief following hydrocortisone acetate is noteworthy.

Serial aspiration without instillation of an agent or with injection of a saline placebo demonstrated that, within 2 days of a given aspiration, the volume

TABLE

COMPARISON OF THE EFFECTS OF HYDROCORTISONE AND HYDROCORTISONE ACETATE INJECTED INTRA-ARTICULARLY

Number of Cases Showing:		Hydrocortisone				Hydrocortisone Acetate			
		Marked Improvement		Moderate Improvement	No Improvement	Marked Improvement		Moderate Improvement	No Improvement
		>5 days	<5 days			>5 days	<5 days		
Changes in Synovial Fluid	Volume	0	6	0	5	4	6	1	3
	Viscosity	0	1	2	6	0	3	2	4
	Mucin Precipitate	0	0	1	10	2	4	2	4
	White Blood Count	0	1	3	7	2	4	4	2
	Per cent. Polymorphonuclears	0	3	1	7	5	10	0	0
Symptomatic Relief		0	0	6	5	5	5	4	1

"Marked" and "moderate" improvement in volume, white blood cell count, and percentage of polymorphonuclears refer to a 50 per cent. and 20 per cent. reduction respectively. "Marked" improvement in viscosity refers to an increase by more than twice, and "moderate" improvement to an increase by one and a half to twice.

The character of the mucin precipitate was judged on the basis of the clot formed after precipitation with acetic acid. It was described as follows:

0, merely a cloudy solution;
1, a few flecks in a cloudy solution;
2, small, friable masses in a cloudy solution;
3, a soft mass in a very slightly cloudy solution;
4, a tight ropy clump in a clear solution. "Marked" improvement refers to a change of +2 or more, "Moderate" improvement to a change of +1.

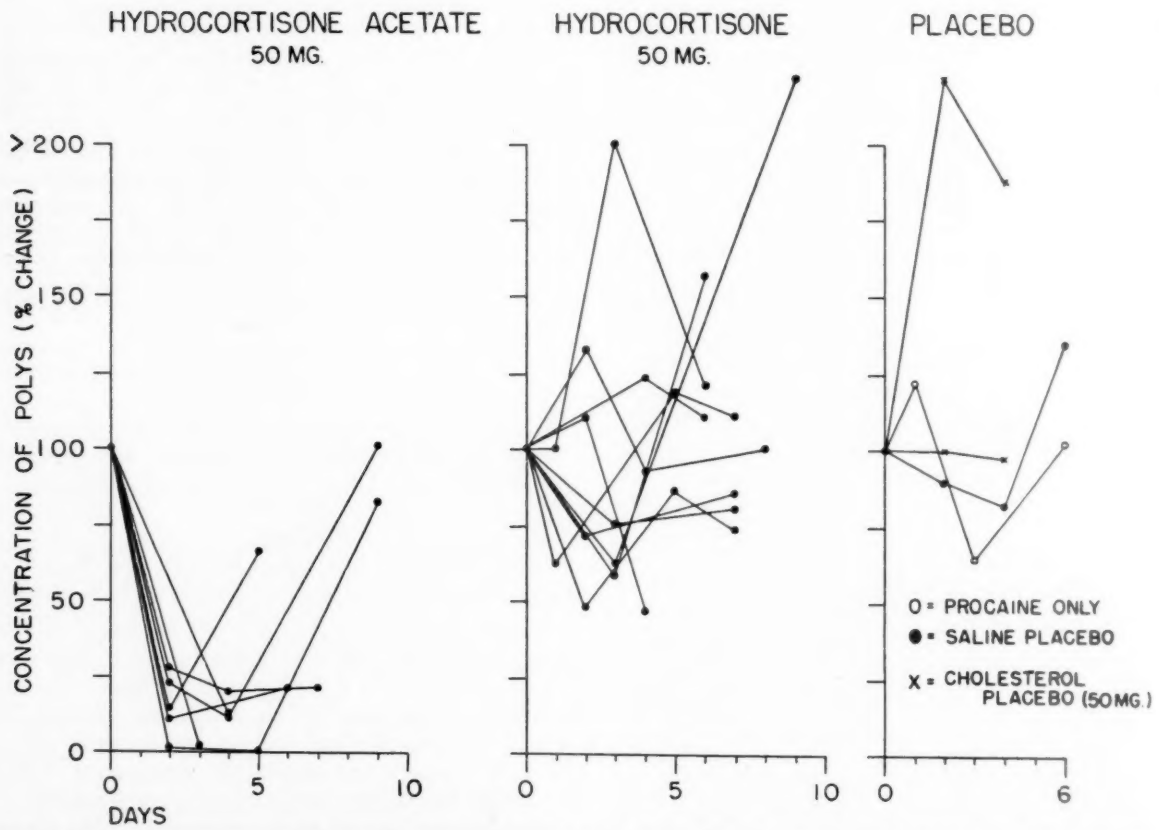

Fig. 1.—Changes in concentration of polymorphonuclear cells occurring after intra-articular instillation of identical doses of hydrocortisone, hydrocortisone acetate, and the indicated placebos. The results designated *procaine* represent a series of diagnostic taps using procaine anaesthesia in the routine fashion.

and characteristics of the fluid were approximately as before. After the administration of both steroid preparations there was a significant decrease in the rate of re-accumulation of fluid. Nevertheless, the duration of effect was clearly greater after the hydrocortisone acetate. Similarly, there was a somewhat higher incidence and magnitude of improvement in both the viscosity and the character of the mucin after the hydrocortisone acetate.

The effect of these agents on the white blood cell count and percentage of polymorphonuclear cells is depicted in Figs 1 and 2. The response to hydrocortisone and the placebo varied widely, but after the hydrocortisone acetate there was a consistent fall in the white blood cell count and especially in the percentage of polymorphonuclear cells. The difference in the response to the two agents is particularly evident in Fig. 1, which records the changes in the absolute polymorphonuclear cell concentration. In contrast with the hydrocortisone and the placebo, the hydrocortisone acetate in every instance produced an unequivocal reduction.

Fig. 3 (overleaf) reveals that, after administration of hydrocortisone acetate, the difference between blood sugar and synovial fluid sugar diminished, whereas after hydrocortisone this difference was usually augmented. This fact, together with the occasional rise in absolute polymorphonuclear concentration, suggests that an irritative response to hydrocortisone can sometimes occur.

The saline placebo was used in three instances without demonstrable subjective or objective change.

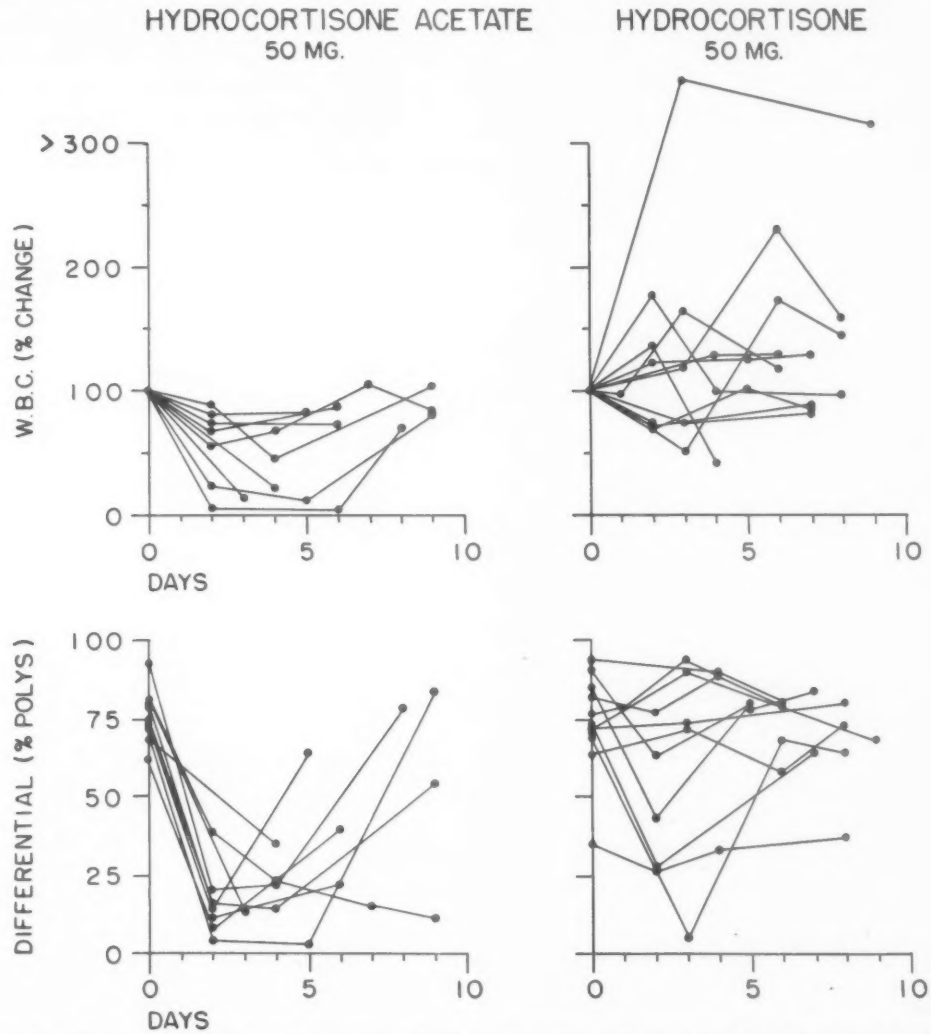

Fig. 2.—Changes in white blood cell count and percentage of polymorphonuclear cells occurring after intra-articular administration of identical doses of hydrocortisone and hydrocortisone acetate (50 mg.). In each series of observations the initial leucocyte count is arbitrarily set at 100 per cent. and subsequent values are related to this initial count.

In two instances the cholesterol placebo produced no adverse response, symptomatic or by analysis of the fluid; in one case its instillation was followed by a striking symptomatic exacerbation, a marked rise in the white blood cell count and percentage of polymorphonuclear cells, and a deterioration of the mucin precipitate. Subsequent instillations of the saline placebo and hydrocortisone were not accompanied by a similar exacerbation.

In the four instances in which eosinophil counts were performed after treatment with 50 mg. hydrocortisone, a fall greater than 50 per cent. occurred either 4 or 8 hrs later. In the two instances in which hydrocortisone acetate was injected the fall was no more than with routine aspiration (15 per cent.).

Discussion

Significant changes toward normal in the synovial fluid appeared more consistently and were of greater magnitude and duration after the injection of hydrocortisone acetate than after hydrocortisone. These results are at variance with the conclusions of Hollander and others (1951), who reported on the basis of clinical evaluation that the two preparations were equally effective.

The patient's subjective evaluation of each agent correlated rather well with the fall in synovial fluid polymorphonuclear concentration and the slow rate of re-accumulation of synovial fluid. That some patients reported symptomatic relief without evidence of associated objective changes probably resulted from the attention associated with aspiration and from lessening of the intra-articular pressure. It is of interest that, in many instances, the patient's estimation of clinical improvement clearly outlasted demonstrable objective changes.

Serial synovial fluid analyses after the injection of the steroids demonstrated considerable variation in degree and duration of effect with the same agent in different patients, and illustrated that any combination of changes may occur. An improvement in the character of the mucin was usually associated

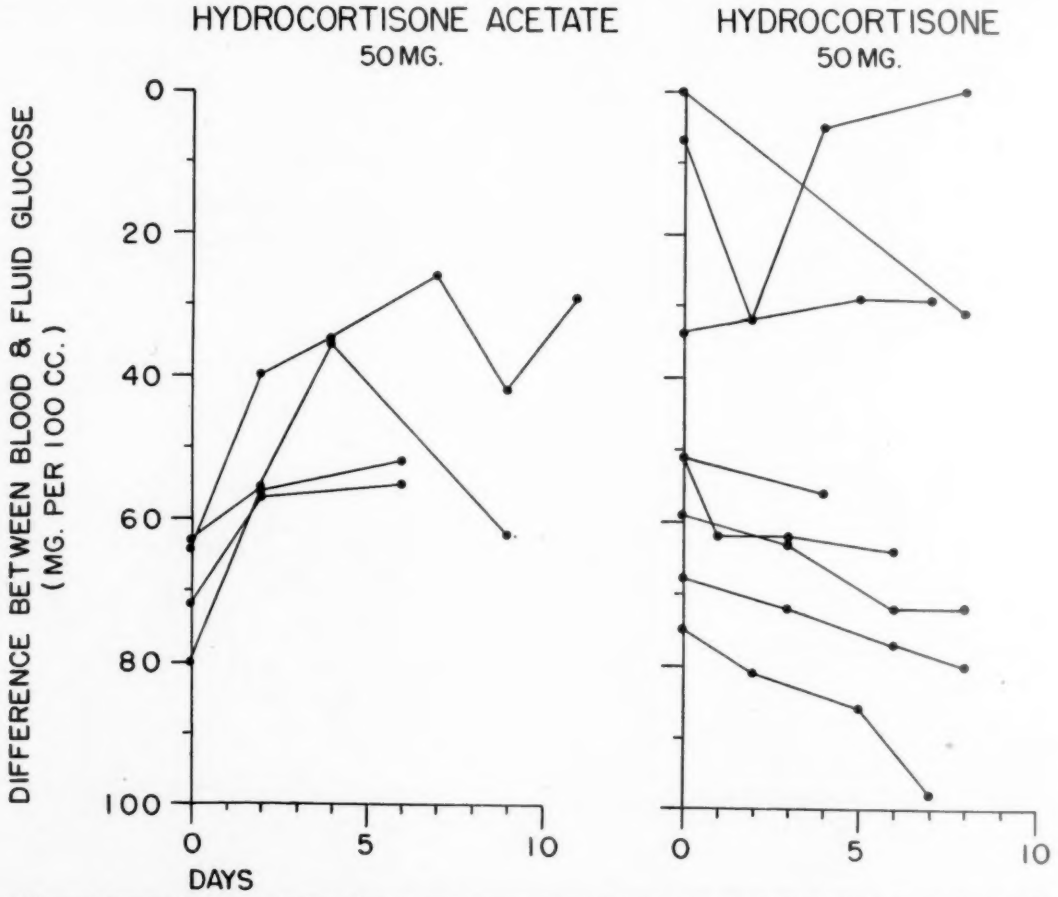

Fig. 3.—Difference between simultaneously determined glucose concentrations in serum and synovial fluid (plotted inversely on ordinate) and change with time. Upward slope indicates improvement.

with a rise in viscosity. These changes, which may mean repolymerization of the hyaluronic acid (Duff and others, 1951), appeared in a few instances after the administration of hydrocortisone, even without an associated anti-inflammatory effect, as measured by a fall in the leucocyte count or in the percentage of polymorphonuclear cells. Ropes (1955) has found that with cortisone acetate there may also occur rises in viscosity without an associated anti-inflammatory effect.

Demonstration of the greater effectiveness of hydrocortisone acetate compared to hydrocortisone may have theoretical connotations. Wilson and others (1953) found that hydrocortisone, cortisone, and their acetates disappeared with equal rapidity from cell-free synovial fluid, despite the fact that hydrocortisone is seven times more soluble in synovial fluid than hydrocortisone acetate (Macek and others, 1952). Zacco and others (1954), while confirming this work, demonstrated that hydrocortisone acetate led to a greater concentration of 17-hydroxycorticoids in the cellular fraction of synovial fluid than did hydrocortisone. However, because they did not find any difference in the clinical effectiveness of these two preparations, they did not attempt to correlate relative insolubility, cellular concentration, and clinical efficacy. The belief that relative insolubility is, at least, an important factor in the effectiveness of steroids placed intra-articularly is supported by our series, in which hydrocortisone was demonstrably less effective than hydrocortisone acetate. The fall in eosinophils which occurred after hydrocortisone, but not after hydrocortisone acetate suggests that the more soluble hydrocortisone entered the systemic circulation.

Summary

(1) The synovial fluid changes after intra-articular injection of an effective steroid preparation are demonstrated by serial analyses, and the variation in duration and pattern of response is illustrated.

(2) Evidence is presented that significant changes in synovial fluid appeared more consistently and were of greater magnitude and duration after injection of hydrocortisone acetate than after injection of hydrocortisone.

(3) It is suggested that the esterified form of the steroid molecule is more effective because it is less soluble.

(4) The usefulness of objective criteria in evaluating an anti-inflammatory response is illustrated.

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Etude en série du liquide synovial dans l'évaluation des agents intra-articulaires

RÉSUMÉ

(1) Par des analyses en série on met en évidence les altérations du liquide synovial après des injections d'une préparation stéroïde active et on décrit les variations de la durée et du type de la réaction.

(2) On présente des données montrant que les altérations significatives du liquide synovial sont plus constantes, plus grandes et plus durables après l'injection d'acétate d'hydrocortisone qu'après l'injection d'hydrocortisone.

(3) On suggère que la molécule stéroïde estérifiée est plus efficace parce qu'elle est moins soluble.

(4) On montre la valeur des critères objectifs dans l'évaluation de la réaction anti-inflammatoire.

Estudio en serie del líquido sinovial en la avaluación de los agentes intra-articulares

SUMARIO

(1) Por medio de análisis seriados se demuestran las alteraciones del líquido sinovial después de inyecciones de una preparación esteroide activa y se describen las variaciones de la duración y del tipo de la respuesta.

(2) Se presentan datos mostrando que las alteraciones significativas del líquido sinovial son mayores, más constantes y duraderas con inyecciones de acetato de hidrocortisona que con las de hidrocortisona.

(3) Se sugiere que la molécula esteroide esterificada es más eficaz por ser menos soluble.

(4) Se demuestran las ventajas de los criterios objetivos en la avaluación de la reacción ani-inflamatoria.

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STUDIES OF THE ACID POLYSACCHARIDE OF THE WHITE CELLS IN RHEUMATIC AND OTHER DISEASES SHOWING ITS SIMILARITY TO THE ACID POLYSACCHARIDE OF AMYLOID

BY

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In a previous investigation (Bassiouni, 1954) injected heparin was isolated from human blood and tissues and endogenous acid polysaccharides from various tissues. The method is summarized in Fig. 1. The isolated acid polysaccharides (A.P.S.) were estimated in terms of beef heparin biologically by their anticoagulant activity and colorimetrically by their dye-binding capacity. The ratio between the anticoagulant activity in units and the colorimetric value in mg. (A/C ratio) characterized the A.P.S. as heparin-like or chondroitin sulphate-like, since in the latter the A/C ratio was very low (between 0-4) compared with 100 for the beef heparin. Paper electrophoresis of the isolated extracts was useful as a confirmatory procedure, since different mobilities were shown by beef heparin, human heparin, and human chondroitin sulphate obtained from cartilage. When 420 ml.-samples of normal human blood were extracted by the same procedure it was found that the plasma was free from the heparin-like substance found in tissues, but that it contained traces of two other acid polysaccharides detected by paper electrophoresis: one moving at the same rate as the chondroitin sulphate of cartilage and another with a lower mobility (Fig. 2, opposite). The normal white cells contained acid polysaccharides (A.P.S.) amounting to 80 μg./420 ml. blood with an A/C ratio of 10, and it was thought to be mainly a chondroitin sulphate-like A.P.S. This A.P.S. could not be detected in most of the normal 4-ml. blood samples that were extracted.

However, when 4-ml. blood samples from rheumatic fever patients were extracted by the same procedure, it was observed during step F of the isolation that the crude precipitate obtained, which is dark bluish in normal blood, included another fine precipitate of a metachromatic reddish-violet

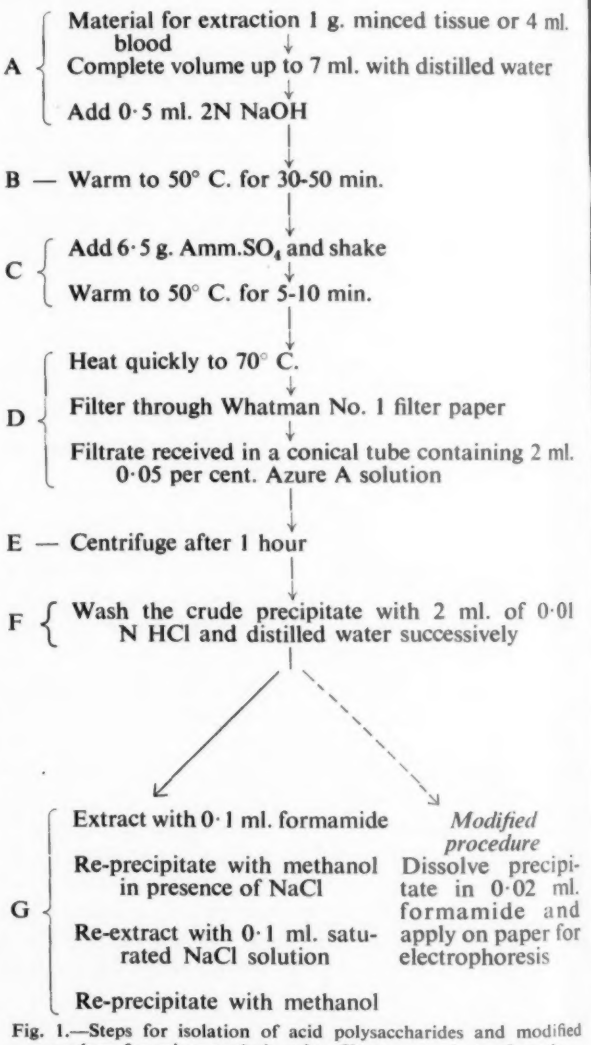
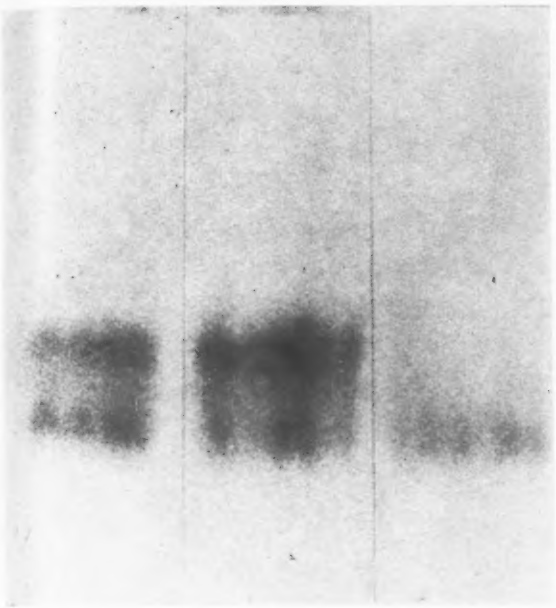


Fig. 1.—Steps for isolation of acid polysaccharides and modified procedure for micro-analysis using filter-paper electrophoresis.



a *b* *c*

Fig. 2.—Paper electrophoresis of A.P.S. extract from two human plasma samples (*a* and *b*), each obtained from 420 ml. blood. Two fairly separated bands were obtained in each experiment compared with chondroitin sulphate of cartilage (*c*).

colour; this suggested that a heparin-like acid polysaccharide might be present.*

As the concentration of the A.P.S. in such a fine precipitate would be very low, extraction and purification by the usual procedure (step G in the diagram) would entail very considerable losses (Bassiouni, 1954) and leave insufficient material for final estimation. In order to avoid these losses a procedure modified especially for use with small samples was adopted, in which the crude complex dye precipitate obtained in step F was dissolved in 0·02 ml. formamide and applied directly on filter paper for electrophoresis.

Method

The detailed procedure is as follows:

The crude dye precipitate which is obtained by centrifuging in the first step of heparin isolation was washed successively with 1 ml. 0·01 N HCl and 0·5 ml. distilled water; then 0·02 ml. of formamide was added and the mixture stirred with a fine glass rod. After warming in a water bath at 50° C. for 5 minutes, it was pipetted off by a micropipette and applied directly on filter paper for electrophoresis using the procedure previously described. Except that the apparatus used was similar to that described by Grassmann, Hannig, and Knedel (1951) and that no chlorobenzene solvent was used, the extracts were allowed to run for 1 hour at a potential gradient of 10 V/cm.

* The basic dye Azure A used gives a bluish violet precipitate with chondroitin sulphate and hyaluronic acid, but a metachromatic precipitate (reddish-violet) with beef heparin—unpublished data.

Results

Extracts from 4-ml. blood samples showed an A.P.S. of this kind in eight out of eleven cases of rheumatic fever, a faint trace in one, and none in two (Table I). A case of "pure" chorea (without rheumatic activity) was negative, but one chorea together with fever gave a faint trace. Four cases of rheumatoid arthritis all gave positive results. Of five samples of normal blood used as controls, four gave negative results, but in one there was a faint trace of A.P.S.

TABLE I

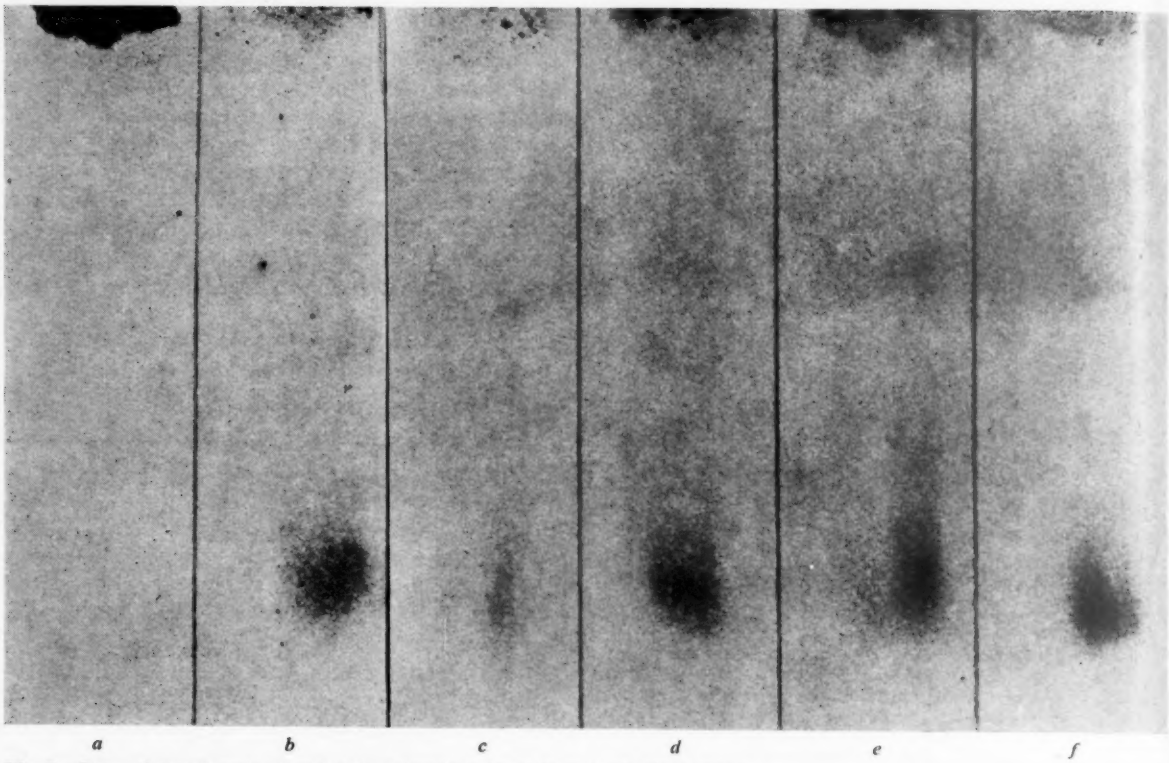
ISOLATION OF AN ACID POLYSACCHARIDE FROM THE BLOOD OF RHEUMATIC PATIENTS AND CONTROLS

Diagnosis	Case No.	Sex	Age	Sedimentation Rate	Acid Polysaccharides detected on Paper Electrophoresis from 4 ml. Blood
Rheumatic Fever	1	F	12	7	+++
	C2	F	13	20	+++
	3	F	13	5	+++
	4	F	13	44	+++
	5	F	16	7	+++
	6	F	15	22	+++
	7	F	12	8	+++
	C8	F	17	15	++
	9	F	28	87	+
	C10	F	15	23	—
	11	F	16	10	—
Rheumatoid Arthritis	12	F	15	11	+++
	13	F	14	10	+++
	14	M	40	44	+++
	15	F	16	31	+++
Pure Chorea with Fever	16	F	15	5	+
	17	F	13	11	—
Normals	18	F	28	—	—
	19	F	19	—	—
	20	F	19	—	—
	21	F	22	—	—
	22	M	38	—	+

C = with carditis.

In other diseases investigated (Table II, overleaf), the most remarkable A.P.S. band was shown in samples of long-standing diabetes, asthma, and acute nephritis; it was also present to the same extent as in rheumatic diseases in other conditions (Fig. 3, overleaf).

Identification of A.P.S.—To identify this A.P.S., 80 ml. blood were collected from patients with rheumatic fever and rheumatoid arthritis. The white cells and plasma were extracted separately, using the full procedure previously described (Bassiouni, 1954). The result shows that the A.P.S. of the white cells from 80 ml. blood gave a value of 38 μg. in terms of beef heparin (colorimetric) and an anticoagulant activity of 1·4 units, thus having an A/C ratio of 37. An A.P.S. was obtained from the plasma of 80 ml. blood which had a



a *b* *c* *d* *e* *f*

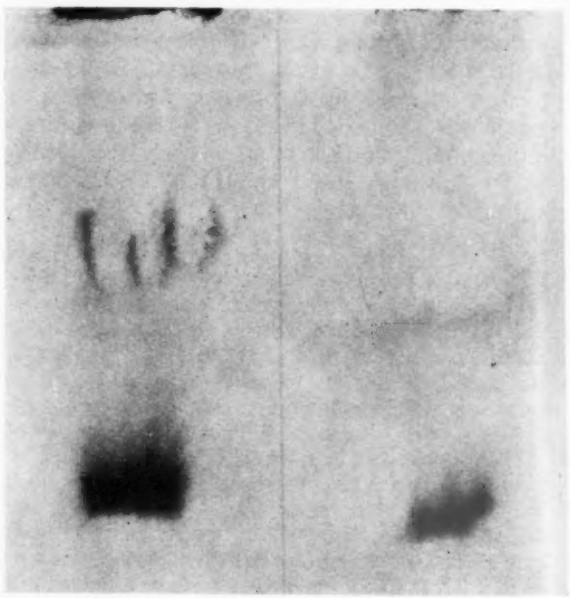
Fig. 3.—Paper electrophoresis of acid polysaccharide isolated from 4 ml. blood from:
(*a*) stone ureter (negative), (*b*) diabetes, (*c*) carditis (rheumatic fever), (*d*) acute nephritis, (*e*) pleural effusion, (*f*) asthma.

TABLE II
ISOLATION OF AN ACID POLYSACCHARIDE FROM 4-ML. BLOOD SAMPLES FROM PATIENTS WITH VARIOUS DISEASES

Diagnosis	Sex	Age	A.P.S.
Stone left kidney	M	53	–
Hypertension	M	63	+
Duodenal ulcer	M	17	+
Asthma	M	44	+
	M	56	+++
Coronary thrombosis ..	M	50	+
	F	77	+
Diabetes	M	55	+++
	M	62	+
Pleural effusion	M	12	–
	F	27	++
Acute nephritis	F	13	++
Mitral stenosis	F	50	+
? Cerebral aneurysm ..	F*	38	+
Bronchiectasis	F	28	–
Pulmonary tuberculosis ..	7 cases		4 positive

* Blood sample 2 ml. only.

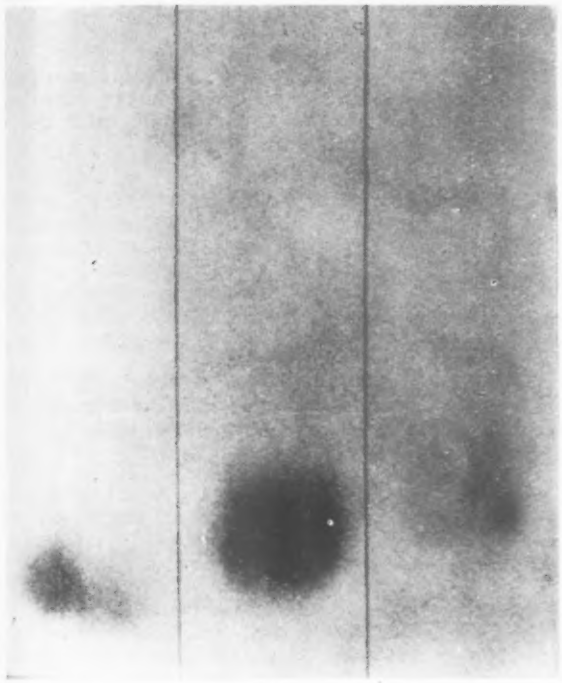
colour value of 20 μg. Another extraction of the plasma and white blood cells (separately) from 40 ml. blood from patients with rheumatic fever only was carried out, and the isolated A.P.S. was run by paper electrophoresis (Fig. 4). The plasma band



a *b*

Fig. 4.—Paper electrophoresis of acid polysaccharide extracted from 45 ml. blood collected from patients with acute rheumatic fever:
(*a*) from white cells, (*b*) from plasma.

was only one-third as dense as that of the white cells. This white-cell A.P.S. had a mobility on filter paper greater than chondroitin sulphate of cartilage, but less than that of beef heparin (Fig. 5). It formed a metachromatic precipitate with the Azure A dye and colour of the compound had a maximum absorption at 580 μg.



a *b* *c*

Fig. 5.—Paper electrophoresis of:
(*a*) beef heparin,
(*b*) white cell A.P.S.,
(*c*) chondroitin sulphate (human cartilage).

An amyloid liver from a long-standing case of rheumatoid arthritis extracted by the usual procedure gave 0·5 mg. A.P.S./g. fresh liver compared with 0·07 mg./g. in normal liver (about seven times the normal content). It had an A/C ratio of 24 and its compound with Azure A had a very metachromatic colour with a maximum spectral absorption at 580 μg. (Fig. 6). These A.P.S. from amyloid liver and from white blood cells resemble heparin more than chondroitin sulphate or hyaluronic acid, since the latter substances have a negligible anti-coagulant activity and their compounds with Azure A after being washed with N/100 HCl and then re-suspended in distilled water are not meta-chromatic and have a maximal spectral absorption at 620 μg. Moreover, the A.P.S. of the white cells, as well as the amyloid A.P.S. (Fig. 7, overleaf), has a greater mobility than chondroitin sulphate, and it

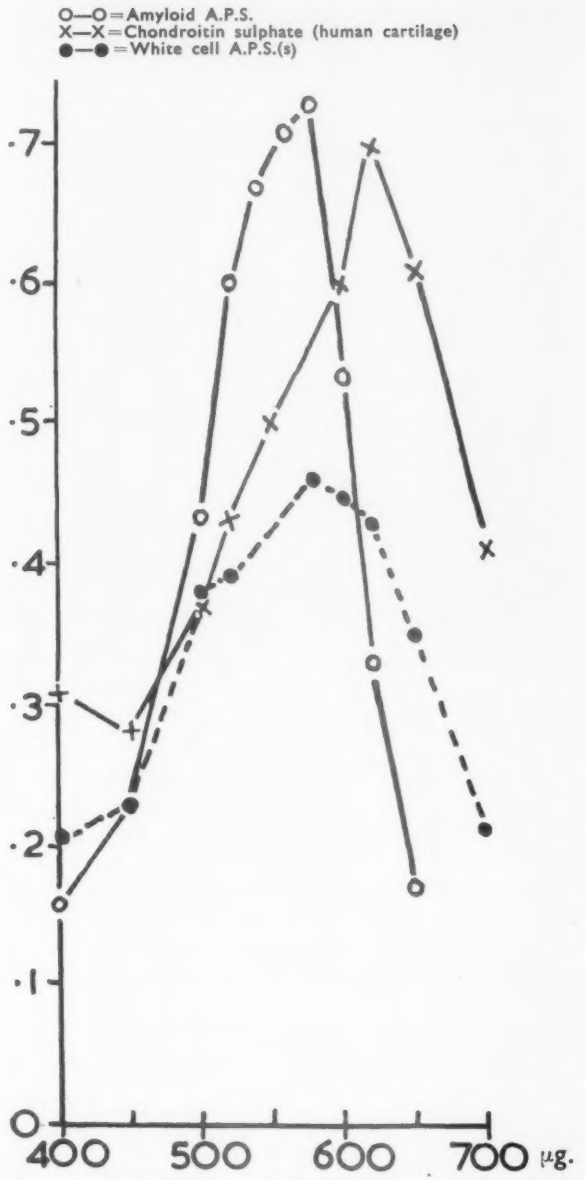
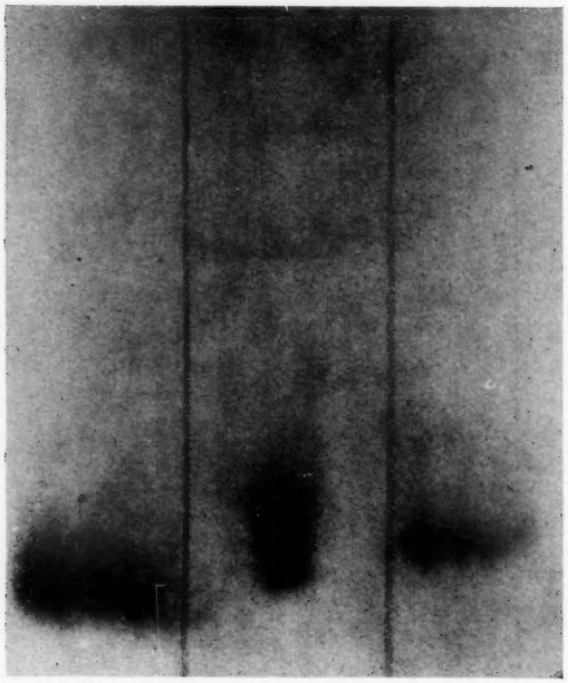


Fig. 6.—Absorption curves of Azure A complexes with amyloid A.P.S., chondroitin sulphate (human cartilage), and white cell A.P.S.(s). In each experiment the dye-acid polysaccharide complex was washed successively with 2 ml. $\frac{N}{100}$ HCl twice and with 2 ml. distilled water once; it was then re-suspended in 4 ml. distilled water. A Unicam photo-electric spectrophotometer was used with absorption vessels of 1 cm. depth and 4 ml. capacity; the latter were calibrated before being used.

must be emphasized that such difference in mobility between the various A.P.S. becomes apparent when they are run for 2 hours, using a potential gradient 10V/cm. Hass (1942) found in his studies of amyloid material that the isolated A.P.S. showed variations



a *b* *c*

Fig. 7.—Paper electrophoresis of:
(*a*) beef heparin,
(*b*) amyloid A.P.S.,
(*c*) chondroitin sulphate (human cartilage).

among different samples of nitrogen and sulphur content. However, he suggested that from these results the A.P.S. was probably chondroitin sulphate, but in the procedure he used for isolating the A.P.S., heparin would be lost in the barium precipitate discarded during the process of purification.

Summary

(1) An acid polysaccharide (A.P.S.) was isolated and identified on paper electrophoresis from 4 ml. blood in cases of acute rheumatic fever and rheumatoid arthritis. It was also detectable in a variety of other diseases and particularly noticeable in a long-standing case of diabetes. It was not present in appreciable amounts in normal blood.

(2) The isolated A.P.S. was found to be mainly derived from the white cells. It has a distinct anticoagulant activity compared with its colorimetric value thus having an A/C ratio of 40. The corresponding values for beef heparin and chondroitin sulphate are 100 and 0-4 respectively. It has an electrophoretic motility on filter paper higher than that of chondroitin sulphate; its complex with Azure A has a metachromatic colour having a maximum absorption at 580 μg. This suggests that this A.P.S. is mainly of a heparin-like nature.

(3) The A.P.S. isolated from an amyloid liver of a long-standing case of rheumatoid arthritis showed similarities to that isolated from the white cells.

I wish to thank Dr. E. G. L. Bywaters for advice and help, and the Empire Rheumatism Council for a grant.

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Etude d'un polysaccharide acide des globules blancs dans la maladie rhumatismale et dans d'autres maladies, montrant sa similarité au polysaccharide acide de la dégénérescence amyloïde

RÉSUMÉ

(1) Un polysaccharide acide (A.P.S.) fut isolé et identifié au moyen de l'électrophorèse sur papier à filtre de 4 c.c. de sang provenant de cas de rhumatisme articulaire aigu et d'arthrite rhumatismale. On le décéla aussi dans un certain nombre d'autres maladies et sa présence fut particulièrement marquée dans un cas de vieux diabète. Dans le sang normal on n'en trouva pas de quantités appréciables.

(2) On trouva que l'A.P.S. isolé provenait surtout des globules blancs. Il est doué d'une action anticoagulante définie en comparaison avec sa valeur colorimetrique, la raison A/C étant 40. Les chiffres correspondant pour l'héparine de boeuf et le sulfate de chondroïtine sont respectivement 100 et 0-4. Sa mobilité électrophorétique sur papier à filtre est supérieure à celle du sulfate de chondroïtine; son complexe avec Azure A a une couleur métachromatique avec un maximum d'absorption à 580 μg. Ces résultats suggèrent que l'A.P.S. est surtout une substance dans le genre d'héparine.

(3) L'A.P.S. isolé du foie amyloïde d'un cas d'arthrite rhumatismale ancienne ressemblait à celui provenant de globules blancs.

Estudio de un polisacarido de los glóbulos blancos en la enfermedad reumática y en otras enfermedades, mostrando su similaridad al polisacarido ácido de la degeneración amiloidea

SUMARIO

(1) Un polisacarido ácido (A.P.S.) fué aislado e identificado por medio de electroforesis sobre papel de filtrar de 4 c.c. de sangre procediendo de casos de reumatismo poliarticular agudo y de artritis reumatoide. Se le encontró también en algunas otras enfermedades y su presencia fué particularmente marcada en un caso de antigua diabetes. No hubo cantidades apreciables en la sangre normal.

(2) Se vió que el A.P.S. aislado procedió ante todo de globulos blancos. Tiene un poder anticoagulante distinto en relación con su valor colorimétrico, la razón A/C siendo de 40. Las cifras correspondientes para la heparina de toro y el sulfato de condroitina son 100 y 0-4 respectivamente. Su mobilidad electroforética sobre papel de filtrar es superior a la del sulfato de condroitina; su complejo con el Azul A tiene un color metacromático con un máximo de absorpción a 580 μg. Estos datos sugieren que el A.P.S. es primeramente una substancia de tipo de heparina.

(3) El A.P.S. aislado del hígado amiloideo de un caso de artritis reumatoide antigua se pareció al derivado de los glóbulos blancos.

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EFFECT OF CORTISONE AND CERTAIN OTHER STEROIDS ON THE PERIPHERAL VASCULATURE IN ARTHRITIS

BY

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The frequent occurrence of a defective peripheral circulation in rheumatoid arthritis has now been well established since the early observations of Pemberton (1923). Moreover, many of the therapeutic measures employed in this and allied conditions result in an increased peripheral blood flow.

After intramuscular injections of adrenocorticotropic hormone (ACTH) changes in the blood flow in the knee joint and an increase in the temperature of the fingers in cases of rheumatoid arthritis were reported by Janus (1950). Improved vasomotor activity after intravenous infusions of ACTH was shown by Beattie and Woodmansey (1953). Although Horwitz, Sayen, Naide, and Hollander (1951) found increased digital temperatures after intramuscular ACTH therapy, they were unable to demonstrate a similar effect with cortisone. We, however, had observed a positive effect after cortisone both on digital temperatures and on thermal response. Moreover, cortisone had earlier been shown plethysmographically by Hines, Wakim, Roth, and Kierland (1950) to produce an increased blood flow in the forearm and legs in cases of scleroderma, and more recently by Catchpole, Jepson, and Kellgren (1954) to cause increased digital blood flow in cases of rheumatoid arthritis.

We are here reporting our work on cortisone and on certain other steroids, investigated not only because they have been administered to patients suffering from rheumatoid arthritis, but also because vascular effects have been attributed to some of them.

Method

The technique employed in these observations was similar to that already in routine use in this Unit, previously described by Woodmansey (1951) and Beattie and Woodmansey (1953). Briefly, it involved skin temperature measurements at various sites (the volar or plantar surfaces of the terminal segments of thumbs and great toes, and the forehead) during a preliminary period of at least 30 minutes, followed by further observations on the exposed limbs during the time of immersion of one leg in a hot-water bath maintained at 44° C. The actual temperatures were recorded with the instrument described in the previous papers. These procedures were carried out, under controlled conditions in a room maintained at a temperature of 18·5°-19·5° C., before and after a course of treatment with the steroid.

Skin temperature, according to Cooper, Cross, Greenfield, Hamilton, and Scarborough (1949) mirrors the rate of blood flow up to about 34° C. The thermal response involves the stimulation by returning warmed blood of the vasomotor centre in the hypothalamus, and the integrity of the sympathetic system on the efferent side, the resulting vasodilatation depending on inhibition of vasoconstrictor tone, which latter is more marked in the lower than in the upper limbs.

Results

Altogether 57 patients (56 females and one male) were included in this survey, 43 suffering from rheumatoid arthritis and fourteen from osteo-arthritis. They were investigated in five groups, each group receiving one of the following steroids: cortisone, testosterone, deoxycorticosterone acetate (DOCA) with ascorbic acid, progesterone, and oestradiol monobenzoate. Only one patient (suffering from rheumatoid arthritis) received two steroids —DOCA with ascorbic acid and progesterone.

During the period of administration of the steroid, the patients received no other specific therapy and no local treatment of the hands and legs was carried out.

Cortisone.—This was administered to twelve patients (eleven females and one male), of whom ten had rheumatoid arthritis and two had osteo-arthritis. Seven patients received oral cortisone—100 mg. on the first day and 75 mg. on the succeeding 5 days. Earlier (1951-52) five patients (four females and one male), all suffering from rheumatoid arthritis, received concentrated courses

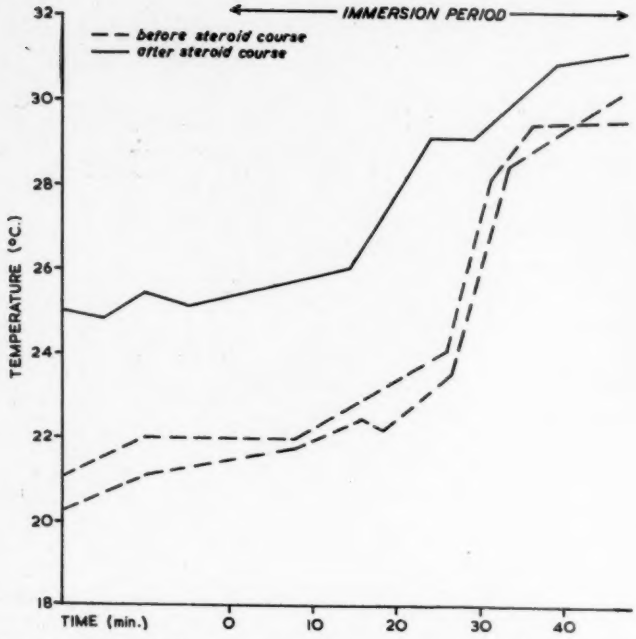

Fig. 1.—Two preliminary tests before, and improved response in one great toe after cortisone treatment.

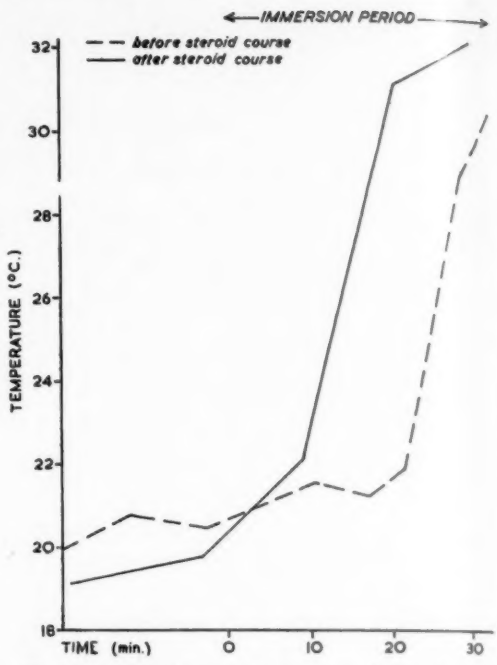

Fig. 2.—Improved response in great toe after cortisone.

parenterally. Four had four injections 8-hourly of 100 mg. and one had six injections 8-hourly of 100 mg. (Figs 1 and 2).

Testosterone.—Testosterone propionate (Testoviron) was administered by daily intramuscular injections of 25 mg. to eleven patients of whom seven had rheumatoid arthritis. In this group, four patients had eight injections, three had seven, two had six, one had five, and one had four (Fig. 3).

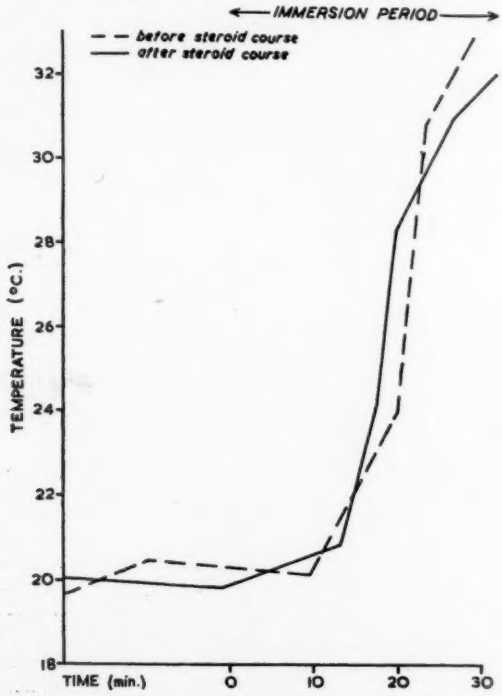

Fig. 3.—No alteration in response in great toe after testosterone.

DOCA and Ascorbic Acid.—Deoxycorticosterone acetate 5 mg. by intramuscular and ascorbic acid 1 g. by intravenous injection were given daily to ten patients; six had rheumatoid arthritis and four osteo-arthritis. Treatment was administered to seven patients for 7 days, to one for 8 days, and to two for 9 days (Fig. 4).

Progesterone.—Daily intramuscular injections of progesterone BP 25 mg. (25 I.U.) were given to fifteen patients, eight suffering from rheumatoid arthritis and seven from osteo-arthritis. In this group six patients had seven injections, six had six, one had five, and two had four (Fig. 5).

Oestrogen.—Oestradiol monobenzoate 50,000 I.B.U. as progynon B 5 mg. was given by intramuscular injection on alternate days for four doses to ten patients (Figs 6 and 7).

The test* revealed the state of the vascular tone during the preliminary resting period, the promptness or otherwise of the response in the exposed limbs to the thermal stimulus and the steepness and extent of the induced rise of temperature.

* The graphs show the temperatures of one great toe before and after immersion of the opposite leg in hot water.

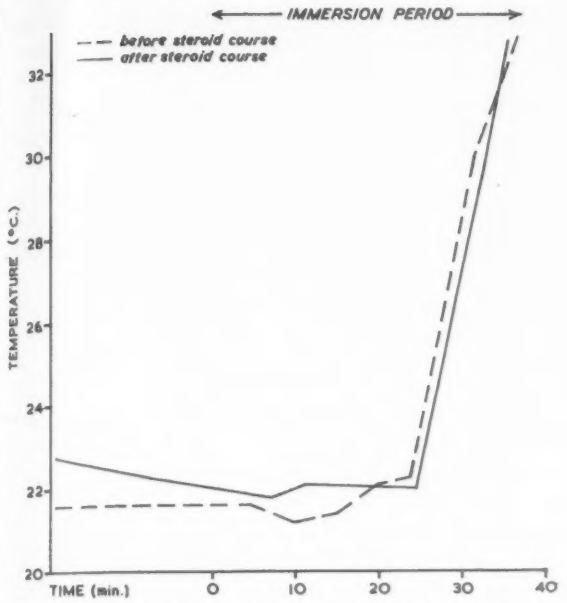

Fig. 4.—No alteration in response in great toe after DOCA with ascorbic acid.

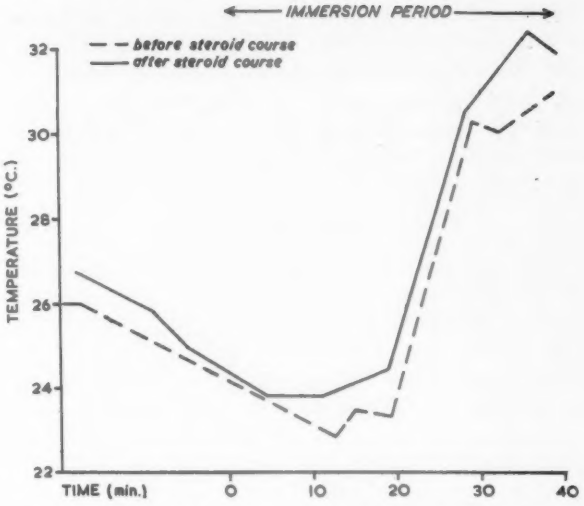

Fig. 5.—No alteration in response in great toe after progesterone.

A numerical assessment of the result of the thermal response test before and after treatment in each case was attempted, as on previous occasions (Woodmansey, 1951; Beattie and Woodmansey, 1953). The thermal response in the foot is considered to be a better criterion for the test than that in the hand. An index representing the gradient of the curve in degrees centigrade per minute was employed. It was calculated by dividing by the time in minutes either the increase in temperature attained from 19° C., *i.e.* room temperature, or if the peak was not reached the temperature rise at the end of thirty minutes' immersion.

A statistical analysis of the results obtained in each group was carried out. The difference in the index before and after treatment was calculated for each patient. The mean difference (*md*), the standard deviation (*s*) and the standard error of the mean difference ($s/\sqrt{n}$) for each steroid group were then obtained. The "t" test $\frac{(md\ \sqrt{n})}{s}$ based on *n*-1

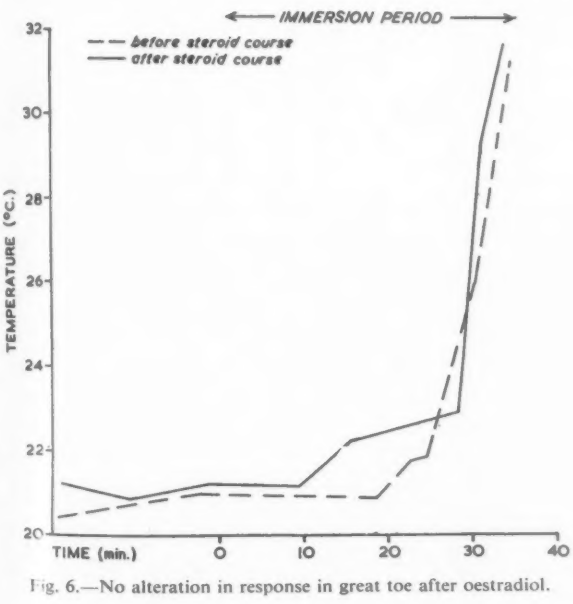

Fig. 6.—No alteration in response in great toe after oestradiol.

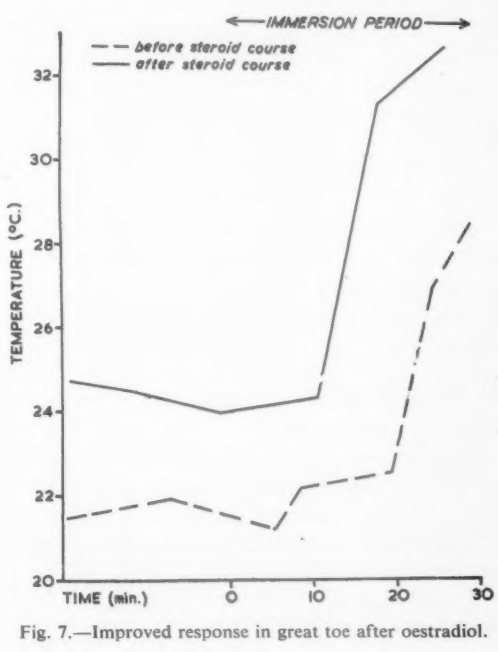

Fig. 7.—Improved response in great toe after oestradiol.

degrees of freedom was applied, giving values of 4·6 for cortisone, 0·06 for testosterone, 1·60 for deoxycorticosterone acetate with ascorbic acid, 1·47 for progesterone, and 1·22 for oestradiol. The only significant result is that which followed cortisone therapy, which is highly significant at the 1 per cent. level.

Discussion

Experimental evidence of the vasodilatating effect of oestrogens and androgens has been brought forward by McGrath (1935), Suzman, Freed, and Prag (1938), Ratschow and Klostermann (1938), and Burckhardt (1946). Clinically, a beneficial effect on peripheral vascular conditions was attributed to oestrogens by Wobker (1940), Walker (1942), and McGrath and Herrmann (1944), though this was denied by White and Smithwick (1941). Good results with androgens were claimed by Edwards, Hamilton, and Duntley (1939), Ernst (1942), and Walker (1942), but Zurrow, Saland, Klein, and Goldman (1942), and Beaser and Massell (1942) were not so optimistic in their views.

These conflicting opinions are understandable in the light of our results with these steroids. Whereas with cortisone every patient responded by showing an improvement in the thermo-vascular regulatory mechanism and status, with the other steroids most of the results were negative, although oestradiol therapy produced improvement in half of the cases.

It is of interest here to consider the effects of treatment by these various steroids in rheumatoid arthritis. Perusal of the literature has shown that where investigations of deoxycorticosterone acetate with ascorbic acid, progesterone, oestradiol or testosterone have been carried out, their therapeutic value was in most cases unproven.

None of our patients receiving steroids other than cortisone experienced any improvement in their rheumatic condition. On the other hand all the cortisone treated patients obtained definite benefit. None of the patients appreciated the nature of the therapy in each case.

In the previous series of experiments (Beattie and Woodmansey, 1953) intravenous infusions of ACTH resulted in an improvement in the thermal response test. In the present series only cortisone produced consistently positive results. Moreover, only these two hormones of those investigated are generally recognized as possessing definite anti-rheumatic activity. Further, of the group of eleven patients receiving DOCA with ascorbic acid, nine subsequently received an intravenous infusion of ACTH and six of these showed an improvement in the thermal response test.

The peripheral vascular effect of cortisone, as previously suggested for ACTH, may be an important factor in the pharmacological action. Horwitz and others (1951) have pointed out that this effect may have resulted from an action either directly on the vessels or on their autonomic control, or indirectly on disease factors that caused excessive vascular tone. The results with the thermal response test with cortisone lend further support to our view that the effect is neurovascular via the thermo-regulatory mechanism.

Summary

The effect on the peripheral vasculature of five different steroids (cortisone, deoxycorticosterone acetate with ascorbic acid, testosterone, progesterone, and oestradiol) has been investigated. Altogether 57 patients (43 rheumatoid arthritics and fourteen osteo-arthritics) were studied in five groups, each group receiving one steroid. Cortisone was the only steroid which consistently produced an improvement in the peripheral vascular status and in the arthritic condition. The peripheral vascular effect may be an important factor in the pharmacological action. It is suggested that this effect of cortisone, like that of ACTH, takes place via the thermo-regulatory mechanism.

We are indebted to Professor S. J. Hartfall for permission to investigate these cases under his care and for his continued interest and encouragement.

We should like to thank Mr. J. D. Sargan, M.A., for his help and advice with the statistical analysis.

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Effet de la cortisone et de certains autres stéroïdes sur les vaisseaux périphériques dans l'arthrite

RÉSUMÉ

On étudia l'effet de cinq stéroïdes différents (cortisone, acétate de deoxycorticostérone avec acide ascorbique, testostérone, progestérone et estradiol) sur les vaisseaux périphériques. En tout 57 malades (43 cas d'arthrite rhumatismale et 14 d'ostéoarthrite) furent repartis entre cinq groupes, chaque groupe recevant un des stéroïdes. La cortisone fut le seul stéroïde à produire constamment une amélioration de l'état vasculaire périphérique et de l'arthrite. L'effet vasculaire périphérique peut être un facteur important de l'action pharmacologique. On suggère que cet effet de la cortisone, de même que celui de l'ACTH, s'obtiendrait par l'intermédiaire du mécanisme thérmo-régulateur.

El efecto de la cortisona y de ciertos otros esteroides sobre los vasos periféricos en la artritis

SUMARIO

Se estudió el efecto de cinco esteroides diferentes (cortisona, acetato de deoxicorticosterona con ácido ascórbico, testosterona, progesterona y estradiol) sobre los vasos periféricos. Un total de 57 enfermos (43 con artritis reumatoide y 14 con osteoartritis) fué repartido en cinco grupos, cada grupo recibiendo uno de los esteroides. La cortisona fué el único esteroide capaz de causar constantemente una mejoría del estado vascular periférico y de la artritis. El efecto vascular periférico puede constituir un factor importante de la acción farmacológica. Se sugiere que este efecto de la cortisona, así como el de la ACTH, obra por medio del mecanismo termo-regulador.

BOOK REVIEWS

Le Rhumatisme. Études cliniques, biologiques, et thérapeutiques (3e Série). By F. Coste and 29 other contributors. 1954. Pp. 388, illustrated. Expansion Scientifique Française, Paris. (30*s*.)

Osbert Sitwell tells us that when writing the *Four Continents* he was tempted to call the book *Voyage round the Inside of My Head.* Professor Coste's books are like voyages round the inside of the Clinique Cochin. The style is both personal and intimate. Original clinical and experimental observations are described and therapeutic results given in detail with case histories and individual charts. To visit Professor Coste's clinic through the pages of these books is a pleasant, stimulating, and instructive experience, though unfortunately one misses the gastronomic and other delights that a sojourn in Paris would provide.

In this third volume Professor Coste and his 29 collaborators discuss five subjects: osteo-arthritis of the hip, gout, viruses in rheumatism, cortisone, and cranial defects.

The classification of osteo-arthritis of the hip into upper, lower, and central lesions is convincingly presented, and one gets the impression that this provides a useful guide to prognosis and management. Benemid is shown to be an effective uricosuric agent in chronic gout, but salicylate therapy is not seriously considered. The Coxsackie viruses and their relationship to epidemic myalgia and other clinical syndromes is fully discussed and the recovery of the virus from human muscle biopsies is reported. Non-specific urethritis is also fully considered. Various therapeutic régimes are discussed in great detail and, though the results are well controlled, in the French sense, by radiological and biochemical studies, no attempt has been made to compare one treatment with another in similar series of cases, so that it is difficult to assess the relative value of the different treatments advocated. Professor Coste's experience is, however, wide and his opinions are authoritative.

J. H. KELLGREN.

Behandlung rheumatologischer Erkrankungen durch Anästhesie. By Egon Fenz. 1955. Pp. 100, 18 illus. *Rheumatismus*, vol. 20. Steinkopf, Darmstadt.

This volume discusses general and local anaesthesia (novocaine) in rheumatic affections, though the indications cited range far outside the field of rheumatology. Much space is taken up by theoretical consideration of the effect of local anaesthesia on muscle tone, muscle wasting, cholinesterase activity, inflammation, etc., but the practical conclusions are based on an experience of 4,116 cases (eight injections each). It is claimed, for instance, that appreciable relief from pain is obtained in cases of ankylosing spondylitis, osteomalacia, and osteoporosis. It is unfortunate that a comprehensive volume of this kind should be marred by a series of poor line-diagrams which offer little help to any prospective operator.

DAVID PREISKEL.

Pelvo-Spondylitis Ossificans. By Ragnar Romanus and Sven Ydén. 1955. Pp. 161, 229 figs. Munksgaard, Copenhagen. (Dan. Kr. 45.)

When studying prostatitis and seminal vesiculitis in 1947, Ragnar Romanus noted that two of his patients also suffered from ankylosing spondylitis. Batson's work on the direct spread of carcinoma cells from the prostate to the region of the sacro-iliac joints made him wonder whether the early localization of ankylosing spondylitis in the sacro-iliac joints was not similarly dependent upon a primary focus (infective) in the prostate. In the following years, he investigated every available male case of ankylosing spondylitis for evidence, past or present, of a genito-urinary infection. He was surprisingly successful in finding such evidence and published his comprehensive thesis on the aetiology of ankylosing spondylitis—with special reference to genito-urinary infection—in 1953. During his study he learnt a great deal about the disease, both from the clinical aspect and, with the help of Sven Ydén, from the radiological aspect. In the book under review Ydén and Romanus have set down their accumulated knowledge and add seventy pages of excellent reproductions of interesting *x*-ray films. What stands out in the book is their contention that the extra-articular bony and connective tissue lesions are at least as important as the lesions of the diarthrodial joints and are just as productive of symptoms. They demonstrate, with *x*-ray films and histological sections, that the ossification that occurs about the vertebrae may follow erosions and remodelling of the cortical bone in a manner similar to that commonly seen in the tuber ischii. In order to give due emphasis to this extra-articular bony disease of the spine and pelvis they propose a new name "pelvo-spondylitis ossificans". It is an attractive name but it is doubtful whether yet another name for the disease will be accepted unless it results from the discovery of its aetiology.

In discussing the aetiology of the disease, Romanus returns to his thesis that it is caused by an infective agent or toxin that spreads directly *via* the blood stream from an infected prostate or seminal vesicle. The patient inherits a susceptibility to the unknown agent and the original genital infection may be silent. This subject occupies little space in the book, and sceptics should not let it deter them from studying the wealth of material and the interesting observations that are so well set forth. All doctors interested in ankylosing spondylitis will appreciate this book and it should find a place in the bookshelves of every department of radiology.

H. F. WEST.

Les Arthroplasties de la Hanche. By Jean Debeyre and Paul Doliveux. 1955. Pp. 91, 15 figs, 12 plates. Éditions Médicales Flammarion, Paris.

The hip joint anatomically is admirably designed for its diverse functions. Its mechanics are complex and the forces brought to bear upon it in normal function are enormous. Latterly surgeons have been so impressed by the mechanics of the joint that they have tended to think and to act as though its components were merely mechanical structures. While recently they have shown a somewhat tardy recognition of the vital vascularity of bones, surgeons still fail to pay sufficient attention to the vital plasticity of bone in its reaction to abnormal stress and to foreign bodies—no matter how inert biologically these may reputedly be. Most of us have, in these matters, much to blame ourselves for. Continental work, particularly recent French work, has as much as any been dominated by the mechanical approach, having been greatly influenced by the beautiful studies of Pauwels. Thus the very sincere work of the Judets, and of Merle d'Aubigné and Herbert, following upon Smith Petersen's pioneer work upon the introduction of inert barrier materials into the hip. Recent experience in Great Britain has resulted in great disappointment, and methods of arthroplasty which promised so well are, because of lack of durability, now being generally discarded. The problem is recognized to be not mechanical but of achieving the impossible fusion of biological tissue with foreign material under stress—biomechanical synthesis.

The whole subject is well reviewed in this present work which commences with an excellent discussion of the mechanical background, largely based upon the work of Pauwels, and then discusses methods of arthroplasty by the Smith Petersen metal cups, and by acrylic prosthesis of the Judet type and its modifications, including the larger specimens which have prolongations into the femoral shaft. Surgical technique is described and a review is given of the follow-up after 200 operations. In the review of results one has some doubts about the length of time after operation, for this is not clearly stated and it does not appear that all cases were examined clinically. None the less, the authors are not at all encouraging. Excellent results at the outset showed later deterioration, so much so that these workers have now abandoned the original Judet prosthesis. The larger prosthesis they regard as the best means of salvaging the unhappy results of previous arthroplasties, and they still hold some hopes for these in other cases for which arthroplasty is indicated. Because, however, of their anxieties, they have not entirely abandoned the use of the Smith Petersen cup. An unhappy story extremely well and fairly told. NORMAN CAPENER.

La Maladie de Bouillaud. Ses complications cardiaques et son traitement. By R. Debré and P. Soulié. 1955. Pp. 148, 25 figs. Expansion Scientifique Française, Paris. (1,200 *fr.*)

This small book is essentially for the practising clinician. The authors are convinced of the great value of hormone treatment in rheumatic fever, particularly for the child seen early in the course of the disease. They therefore devote the first section (by Debré, Mozziconacci, and Keller) to the diagnosis of rheumatic fever in the early stage of its development; this is followed by a section by Soulié and Nouaille on rheumatic carditis, in which its natural history and development is described.

A section then follows along orthodox lines on the value of the estimation of anti-streptolysin O in the serum. The main section is on the hormonal treatment of the acute phase of rheumatic fever (by Debré, Mozziconacci, and Caramanian) and deals with 267 cases seen in a period of 3½ years, 23 of them having severe carditis, 131 carditis, and 113 acute rheumatism but without carditis. Of the first group, six children died. There were no major complications of treatment. ACTH was used in a few cases where rapidity of action was needed. Cortisone was given more generally, in a dosage of 250 mg. for the first 2 days and then at 200 mg./day for children over the age of 10: between 5 and 10 years the dose was 50 mg. lower.

The duration of treatment was decided on an individual basis, but in general was about 10-15 days, being prolonged up to 1 month or 6 weeks in resistant cases and until the sedimentation rate fell below 20 mm. per hr. No control group was studied.

The final section deals with the problems of convalescence as observed by Labesse and Dagonet at the Hôpital de Convalescents de la Roche-Guyon. It is a full and sensible account of the care of these children dealing with such problems as rest, antibiotics, and the need for continued observation. The book can be highly recommended and is full of interesting information on the practical management. E. G. L. BYWATERS.

Gold Treatment of Rheumatoid Arthritis. By Folke Bohman. 1954. *Acta genetica et statistica medica*, Suppl. 3, vol. 5. Pp. 164, 62 tables. S. Karger, Basel. (17.30 *Swiss francs.*)

The first chapter of this book consists of a useful and fairly comprehensive review of the world literature on the subject of chrysotherapy in rheumatoid arthritis. In subsequent chapters, Dr. Bohman presents the results of a study carried out at the Pension Board's Hospital at Nynäshamn between 1939 and 1944 with a follow-up between 1946 and 1950. The progress of 502 patients who had received gold is compared with that of 362 patients who received "other treatment"—mainly physiotherapy. In a final section the results of certain combined therapeutic regimes, using gold and cortisone, and gold and Salazopyrine are briefly discussed. However, since these two groups combined only comprise 62 patients, the author is rightly reticent about drawing any conclusions. By contrast, the results of the main trial are presented in very great detail, each analysis being subjected to statistical scrutiny. The conclusions are uniformly favourable to chrysotherapy by all the criteria used, save for the vital one that the working capacity of these patients did not seem to be improved. The author attempts to explain this in terms of the initial

severity of the disease in these patients and has introduced a system of "weighing" the results, which the reviewer found difficult to follow.

In common with all ambitious clinical trials of this nature, many technical deficiencies are apparent in the methods used, which must detract to some extent from the conclusions drawn. Thus: the follow-up data was obtained by means of a written questionnaire rather than by personal examination. The notorious inaccuracies which inevitably occur in subjective evaluations of this nature do not need to be stressed. Furthermore, although it is not explicitly stated, it seems that many of the earlier cases were selected and evaluated retrospectively from routine hospital records and were not regarded as research cases *a priori*. Personal experience suggests that records taken in this way—presumably by many different observers—are seldom sufficiently accurate for subsequent comparisons. Finally, the exact criteria used for "scoring" the joint pathology is not made clear. For example, joints which were ankylosed were given the maximum score (p. 50), whereas those exhibiting effusions were rated lower. This seems almost calculated to give a false impression, since the former condition is irreversible whilst the latter is at least potentially reversible. It would be more logical to note ankylosis as a *fait accompli* and only to score those features which the drug could reasonably be hoped to influence.

Despite these criticisms of points of detail, this remains a useful and painstaking study which contributes further significant but inconclusive evidence to support those who maintain that gold therapy can alter the natural history of rheumatoid arthritis. The presentation is good, but the English translation in places could be improved. JOHN H. GLYN.

Artrite Reumatoide. By Jacques Houli. 1953. Pp. 264, illus. Industrias Quimicas Schering S/A, Rio de Janeiro.

Many doctors, especially those living in the temperate zones, have suffered from the delusion that rheumatoid arthritis is an uncommon disease in the tropics. Dr. Houli points out that in Brazil alone (population about 48,000,000) there are over half a million burdened with the disease. There is much justification, therefore, for this monograph in the Portuguese language. It is good to see a chapter on the historical aspect; the remaining ones deal quite adequately with the subject, and the material is well classified. There is a wealth of statistical data and appropriate photographic reproductions are included. Although there is little new for the rheumatologist, the general physician would most certainly benefit from digesting its contents. The bibliography is more than adequate. PAUL B. WOOLLEY.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

THIRD EUROPEAN RHEUMATOLOGY CONGRESS, 1955

The third European Rheumatology Congress was held from June 13 to 17 at Scheveningen, in Holland, under the presidency of Dr. PEDRO BARCELO (*Spain*).

One of the main themes was the association of rheumatism and social medicine. Prof. K. M. WALTHARD (*Geneva*), among others, described the services and plans for the future in Switzerland. A small survey had been carried out in one of the most rural Swiss valleys, where it was found that degenerative arthritis was extremely common. This was ascribed to the hard manual labour undertaken by the inhabitants.

Prof. NANA SWARTZ (*Stockholm*) presided over a session devoted to the evaluation of therapy, at which Dr. J. J. R. DUTHIE (*Edinburgh*) described the significant factors in reaching a prognosis in rheumatoid arthritis. He based his opinion on a follow-up study of 282 patients seen at an average of 4 years after discharge from hospital. Patients admitted to hospital within one year of onset had a much better prognosis than those admitted at a later stage. Functional capacity at follow-up deteriorated progressively the longer the duration of the disease before admission, and those patients in whom the disease ran a rapidly progressive course in the first year fared appreciably better in the long run than those in whom it started more insidiously. The importance of studies on the natural history of rheumatoid arthritis, particularly now that the necessity for evaluating new drugs has arisen, was admirably stressed in this paper.

During a session on connective tissue, with Prof. F. COSTE (*Paris*) in the chair, Dr. L. E. GLYNN (*Taplow*) described studies suggesting that widespread alteration in connective tissue occurs in patients with rheumatic fever. Increased permeability of the connective tissue was shown by the delay in the reconstitution of the dermal barrier after an injection of hyaluronidase. Dr. G. ASBØE-HANSEN (*Copenhagen*) discussed the hormonal control of mesenchymal tissue. He had found that the individual elements of all connective tissue respond alike to the same hormones. In the course of a few hours endocrine secretions altered the physicochemical balance and water-binding capacity of the tissues, and accumulation of mucopolysaccharides reduced tissue permeability. Thyroid hormone inhibited wound healing. The adrenal cortical hormones regulated the function of the mast cells: these cells, believed to be the source of ground-substance components, underwent such changes as degranulation and vacuolation, and their sulphur turnover was altered, while the release of hyaluronic acid, heparins, and histamine might also be affected. Corticotrophin had the same effect. In patients with rheumatoid arthritis the mast cell count in

the synovial tissue was increased, but this rise was inhibited by cortisone and corticotrophin.

Dr. W. S. C. COPEMAN (*London*) presided over a session devoted to papers on disk degeneration and osteo-arthritis of the spine. Prof. STEN FRIBERG (*Stockholm*) showed that the lower lumbar disks disintegrate earlier and to a greater extent than had previously been supposed, and that a negative radiograph did not preclude even advanced disintegration. Deforming arthritis in the intervertebral joints occurred mainly at the level of the disk trouble which was found in 50 per cent. of patients with chronic lumbar pain. In a large series of such patients, 20 per cent. reported an injury accepted for insurance compensation, 20 per cent. gave a history of minor strains such as lifting, and 60 per cent. had no obvious exciting cause.

The delegates were entertained by the Government of the Netherlands in the Hall of Knights at The Hague, and by the Corporation of Amsterdam at the Rijksmuseum after a trip on the canals. The excellent organization of the Nederlandse Vereniging van Rheumatologen was greatly appreciated by the 800 delegates of the European League against Rheumatism who attended the Congress.

DR. J. VAN BREEMEN'S 80TH BIRTHDAY

During the course of the 3rd European Congress of Rheumatology a meeting was held in the Royal Netherlands Academy of Sciences and Letters in Amsterdam at which a large number of the "elder statesmen" of the European League paid tribute to its founder, Dr. van Breemen, who afterwards, with his wife, entertained the company. It was announced that the Royal Netherlands Government had put a large sum of money at his disposal to mark the occasion, and to pay tribute to his pioneer work in rheumatology. It was provisionally decided that this should be used to endow periodic conferences of experts who would meet in Amsterdam by invitation to discuss predetermined problems of importance in this field. The further details of the scheme were placed in the hands of a committee who will report in due course. W.S.C.C.

HEBERDEN SOCIETY

Clinical Meeting held at the Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases on July 1 and 2, 1955. The President, Professor R. E. Tunbridge, took the chair at the first session:

DR. G. R. NEWNS, of the Sheffield Centre, presented some observations on the rehabilitation of the rheumatoid cripple. He reviewed the changes in functional status of 238 patients with rheumatoid arthritis first seen during a period of 12 months. Particular attention was paid to the results of treatment in 28 patients who required correction of deformity in weight-bearing joints: 73 per cent. had maintained some improvement when examined 3 to 4 years later.

In the discussion the importance of supervising the continuation of treatment by active exercises in the home, and the employment of trained physiotherapists for this purpose was stressed.

DRS E. LOCKEY and A. J. ANDERSON, of the Westminster Hospital, discussed the results of estimating urine and serum mucoproteins in rheumatic diseases. In rheumatoid arthritis the concentration of serum mucoprotein was usually higher than normal; the level was about the same as in other types of inflammatory disease, but below that encountered in cancer. There was no obvious difference between the results in rheumatoid arthritis and ankylosing spondylitis. Information about urine mucoprotein levels was scanty, but some correlation with serum levels was found. There was a very rough correlation between serum mucoprotein values and the erythrocyte sedimentation rate, and a definite one, absent in other diseases, between the former and the flocculation tests. Evidence was presented that mucoprotein is not responsible for the agglutination phenomenon which forms the basis of the Waaler-Rose test.

In the discussion, speakers emphasized the difficulty of correlating abnormalities which are themselves not specific for a single disease.

DR. T. L. PILKINGTON, of the Middlewood Hospital, Sheffield, had brought more precise methods than most earlier observers to a study of the incidence of rheumatoid arthritis in psychotic conditions. His preliminary findings indicated a low incidence (less than 0·7 per cent.) of rheumatoid arthritis in schizophrenia—contrasting with a normal incidence in mental deficiency and in epilepsy.

It was suggested in the discussion that a study of this nature might usefully include a comprehensive radiological survey, and that the effect of prolonged inactivity might play a part in the low incidence in schizophrenics.

DR. H. F. WEST, of the Sheffield Centre, described his recent experiences with the new synthetic steroid, Meticorten. In three patients given Meticorten instead of hydrocortisone (systemic) or ACTH a reduction in blood pressure and a loss of retained water was observed, but two developed severe epigastric pain. Observations on the ability of this steroid to suppress adrenocortical activity were mentioned.

In the discussion a fourfold enhancement of anti-inflammatory activity shown by Meticorten over that of cortisone was described. An unexpectedly favourable response in a case of rheumatoid arthritis with advanced amyloid nephrosis was mentioned, and the reduction in blood pressure and oedema on changing from cortisone to Meticorten was confirmed.

The second session was presided over by Dr. W. S. C. Copeman.

PROF. D. H. COLLINS, of the University of Sheffield, described the pathological conditions revealed by routine examination of the lumbar vertebrae in one hundred consecutive, unselected, autopsies. Metastatic carcinomatous deposits were found in eleven cases, osteoporosis in nine, Paget's disease in three, leukaemic deposits in two, and myeloma in one. The incidence of osteoporosis rose from 7 per cent. in the seventh decade to 21 per cent. in the eighth and 63 per cent. in the ninth. The frequency of unsuspected Paget's disease in pathological material was stressed.

DR. H. F. WEST surveyed a series of fatalities and adverse reactions in 52 cases of rheumatoid arthritis treated with cortisone for periods of from 1 to 5 years. In six patients who died during treatment, amyloid disease was found in two and polyarteritis nodosa in a third. As both these conditions can occur in association with rheumatoid arthritis their relation to cortisone therapy is difficult to appraise. One patient was found at autopsy to have severe myocardial fibrosis, and two others died, one suddenly, of pneumonia. Among the non-fatal adverse reactions psychotic disturbances occurred in three cases. Injections of corticotrophin occasionally produced anaphylaxis.

In the discussion of this paper, Dr. Oswald Savage commented on six fatalities which had occurred among ninety patients treated with cortisone for long periods.

DR. R. SOUGIN-MIBASHAN, of the Post-Graduate Medical School of London, reviewed some clinical and metabolic aspects of gout in South Africa, where the condition seems to be surprisingly common. The disease occurred with about the same frequency in the white and coloured populations of Cape Town, but was almost unknown in Negroes. Fifty patients were treated with probenecid, untoward reactions being confined to occasional slight epigastric discomfort in four. The clinical effects included disappearance of pain and stiffness (after 4-8 weeks), reduction in the size of tophi and a return of movement in fixed big-toe joints (after 6-9 months), and occasional radiological improvement. Colchicine was given during the early stages of treatment with probenecid to prevent the acute attacks which tend to occur at this time.

DR. J. S. LAWRENCE, of the Walkden Miners' Clinic, discussed the results of a survey of occupational factors in degenerative joint disease. Miners and dock workers had a high incidence of disk degeneration in the lower dorsal and lumbar spine, and also of osteo-arthritis in the knees. Degenerative changes in the cervical spine showed, however, no predilection for miners. Heavy manual work, especially in the stooping position, was a factor in the development of disk degeneration in the lumbar region. Damp working conditions were associated with an increased frequency of symptoms, but not of radiological changes. The survey showed forcibly the heavy toll taken by this type of disease in terms of disability among miners.

The Annual General Meeting will be held on November 25 and 26, 1955, at the Royal College of Surgeons, London.

The Heberden Oration, which was to have been given on October 21, 1955, at the Royal Society of Medicine, London, will *not* now take place.

EMPIRE RHEUMATISM COUNCIL

SUMMARY OF THE E.R.C. CORTISONE/ASPIRIN TRIAL*

The present Cortisone-Aspirin trial was born of a desire to repeat the M.R.C. trial with continuous rather than interrupted therapy in a less narrowly selected group of cases. It seems that in general much the same results have been obtained as in the former trial and that the aspirin- and cortisone-treated groups showed no significant differences when assessed after 6 months and after 1 year. The trial continues, as most of the patients are still on treatment, and we hope to run on to the end of the third year.

The *x*-ray work, which has been most painstakingly done by Dr. Ifor Williams, has been most informative; for, quite apart from the result, it represents a serious attempt to assess radiological changes over a relatively short time in rheumatoid arthritis. Many difficulties have been encountered, but a good basis has been laid for any further similar studies. Dr. Williams found that for practical purposes hands and wrists were the most useful joints to assess in a scheme like this, and that in the hands bony erosions were the most helpful indication of progression. Surface and pocketed erosions accounted for 87 per cent. of the points of assessment.

Dr. Lewis-Faning, who has done an immense amount of statistical work, states that the two groups of patients appear to have been truly comparable, in that at the outset they were similar in all relevant characteristics, and the unavoidable withdrawal of some patients from each group did not affect the issue. Progress has been strikingly parallel in every respect in the cortisone- and aspirin-treated groups. It is of interest that improvement in both groups was greater in the first 6 months than in the second, and it will be interesting to note further progress at the end of 2 and 3 years.

We thank the participants from all nine centres, and Messrs. Merck and Co. for supplies of cortisone.

F. DUDLEY HART.

* Full details of the first year of the trial will appear in the December issue.

CANADIAN RHEUMATISM ASSOCIATION

ANNUAL MEETING, 1955

At the Annual Meeting of the Canadian Rheumatism Association, held at the Royal York Hotel, Toronto, on June 24 and 25, 1955, under the presidency of Dr. Donald C. Graham, the following papers were presented:

Ultra-Sound Wave Therapy in Soft-Tissue Rheumatism. By Walter Ruhman (*Montreal*).

Sjögren's Syndrome—An Ocular Complication of Rheumatoid Arthritis. By A. J. Elliott (*Toronto*), by invitation.

Spontaneous Rupture of the Extensor Pollicis Longus Tendon in Rheumatoid Arthritis. By Glen A. McDonald (*Toronto*), by invitation.

Surgical Procedures of Value in the Management of Rheumatoid Arthritis, A Review of Toronto General Hospital Cases. By W. R. Harris (*Toronto*).

Medical and Social Factors of Importance in the Prognosis of Rheumatoid Arthritis. By Malcolm Thompson (*Boston and Edinburgh*), by invitation.

A Clinical Review of Rheumatic Diseases, Diagnosis and Treatment. By Douglas Taylor (*Toronto*).

Assessment of Therapeutic Agents in Rheumatoid Arthritis. By Leslie Mandel (*Ottawa*).

Pigmented Villonodular Synovitis. By J. N. Swanson (*Toronto*).

The Painful Shoulder Syndrome in Sanatorium Patients. By H. S. Robinson (*Vancouver*).

One session was devoted to a joint meeting with the Canadian Heart Association:

Cardiac Involvement in Rheumatoid Arthritis and Ankylosing Spondylitis. By Hugh Smythe and Donald C. Graham (*Toronto*).

Observations on the Use of Predisone (Metacortandracin) in Rheumatic Disease. By Phillip S. Rosen, Wallace Graham, A. A. Fletcher, Donald C. Graham, M. A. Ogryzlo, J. N. Swanson, and Annjane Carter (*Toronto*).

Clinical Observations in Rheumatic Diseases Treated with Metacortandracin. By R. Dussault, J. A. Blais, R. Demers, J. Durivage, L. Francoeur, L. Long, and deG. Vaillancourt (*Montreal*).

Serious Toxic Manifestations of Prolonged Hydralazine (Apresoline) Therapy. By J. D. Morrow (*Toronto*), by invitation.

Selection of Patients for Mitral Commissurotomy. By Paul Wood (*London, England*), by invitation.

Favourable comments were expressed in discussion about the advantages of the combined meeting with the Canadian Heart Association and the greater participation by our orthopaedic members in this year's programme. We were also privileged to hear from two British speakers and from our French-speaking Canadian members, whose paper bodes well for the 1956 meeting in Quebec City. The following Executive Committee was elected for 1955-1956:

Past President: Dr. D. C. Graham (*Toronto*).
President: Dr. H. Garfield Kelly, *Kingston General Hospital, Kingston, Ontario.*
First Vice-President: Dr. F. W. Hurlburt (*Vancouver*).
Second Vice-President: Dr. J. F. L. Woodbury (*Halifax, Nova Scotia*).
Secretary-Treasurer: Dr. J. B. Frain, *Winnipeg Clinic, Winnipeg*, 1, *Manitoba.*
Other Members: Dr. J. G. Johnson (*Montreal*).
Dr. R. Dussault (*Montreal*).

UNIVERSITY OF HAVANA

Summer School, 1955

The success of the course in rheumatology held in 1954 has encouraged the organizers to enlarge the scope of the course in 1955. An extensive theoretical and clinical programme was held at the Nuestra Señora de la Mercedes Hospital under the direction of Dr. Victor Santamarina of the Liga Cubana contra el Reumatismo. The following specialists were responsible for various aspects of the course: Dr. F. Salas Panisello (anatomy and pathology), J. Alonzo Suárez (radiology and physiotherapy), M. Delgado Comas (gastro-enterology), H. de la Torre Campos (cardiology), E. Roces García and A. Lopetegui Sanchez (rheumatology).

ACTA RHEUMATOLOGICA SCANDINAVICA

We are glad to welcome a newcomer of high standard to the ranks of journals which deal with the rheumatic diseases. The series of Scandinavian journals covering special fields of medicine and surgery which are collectively entitled the "Acta" has just issued the first number of the *Acta Rheumatologica Scandinavica.*

It will appear four times a year and will publish papers in English, French, or German, with summaries in all three languages. The subscription rate is 72*s.* per annum, and the publisher's address is Drottninggatan 6, Stockholm C.

It is the official organ of the united rheumatological societies and institutes of the Scandinavian countries, and its Editor-in-chief is Professor G. Edström, the Director of the Department of Rheumatism in the University of Lund, Sweden. Amongst other distinguished members on the Editorial Board are Professors Brøchner-Mortensen, Holten, and Jarløv, who are well known to all members of the International and European Leagues against Rheumatism as teachers of internal medicine who have been pioneer sponsors of the sub-specialty of rheumatology within this field. We wish the new Journal a long and successful life.

W.S.C.C.

Ann. rheum. Dis. (1955), **14**, 304.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Diagnostic and Therapeutic Aspects of Rheumatic Activity. (Les aspects diagnostiques et les aspects thérapeutiques de l'activité rhumatismale.) RAYNAUD, R., ROBERT D'ESHOUGUES, J., MINICONI, P., FERRAND, M., PASQUET, P., and PASQUET, V. (1954). *Sem. Hôp. Paris*, **30**, 4051. 2 figs.

The disease process of rheumatic fever may be active in the absence of any clinical manifestation. After subsidence of an acute episode, it may continue quietly for months or even years, during which time irreversible changes in the heart are established. From the authors' detailed study of fifty cases of rheumatic fever the most interesting conclusion emerges that changes in the level of serum mucopolysaccharides (glucoproteins), revealed by paper electrophoresis, provide the most reliable criterion of this activity. After migration of the serum glucoproteins under electrophoresis, the paper bands are treated with a staining reagent which marks their distribution and extent and clearly reveals any change from the normal. The result is referred to as a "glucidogram".

All fifty patients studied showed some sign of activity; in 41 cases there was an acute attack, in four there was active rheumatic carditis, and five were cases of well-compensated valvular disease showing either an increased P–R interval in the electrocardiogram, or an increase in erythrocyte sedimentation rate, or both. In all these cases without exception the glucidogram showed an important increase in the α_1 and α_2 glucoprotein fractions. Thus the surface on the glucidogram occupied by the α_1 fraction was increased up to 200 sq. mm. (normal 50 to 100 sq. mm.) and that corresponding to α_2 was 400 sq. mm. instead of the normal 150 to 200 sq. mm. This was the one constant feature of all the authors' cases, and although the degree of increase in the α_1 and α_2 glucoprotein fractions did not run parallel with the clinical severity, the authors believe that it is an expression of the potential activity of the disease, and therefore of the greatest prognostic value.

In 32 cases repeated electrophoretic tests were made during treatment, which in twenty cases consisted in administration of cortisone, in eleven of sodium salicylate, and in one of aspirin only. Cortisone treatment was continued daily for 6 weeks in progressively decreasing doses from 300 mg. in the first few days to 100 mg. during the 4th, 5th, and 6th weeks, being followed by aspirin in doses of 4 to 6 g. daily for 3 to 6 months. Of the eleven patients treated with sodium salicylate, nine received 6 g. daily for 3 weeks, the drug being given intravenously in a solution containing glucose; this was followed by oral administration of sodium gentisate, 10 g. daily, for several weeks. The remaining two patients received salicylates both intravenously and orally. The clinical response was almost identical in these two treatment groups. In thirteen cases the glucidogram became normal in less than 4 weeks, in seven cases the period required was from 5 to 7 weeks, while in a further seven the serum disturbance persisted beyond the 7th week (five cases could not be followed up). These results are considered comparable with the impression of the evolution of untreated rheumatic fever.

Their observations lead the authors to three main conclusions:

(1) Neither sodium salicylate, nor aspirin, nor cortisone has any action on the activity of the rheumatic process itself.

(2) The glucidogram is the only reliable criterion of this activity, and by means of it treatment should be controlled; this is especially important in cases treated with cortisone, since the hormone affects the erythrocyte sedimentation rate and thus destroys its value as a criterion of activity.

(3) In all attacks of rheumatic fever therapeutic measures should continue as long as the glucidogram remains abnormal, even though the clinical signs, the electrocardiographic findings, or any other laboratory test may seem to suggest that they could be stopped.

Kenneth Stone.

Place of Phenylbutazone in the Treatment of Acute Rheumatism. (La place de la phénylbutazone dans le traitement actuel de la maladie de Bouillaud.) ABLARD, G., LARCAN, A., HURIET, C., GILGENKRANTZ, J. M., and GIRARD, C. (1954). *Presse méd.*, **62**, 1865. 18 refs.

The authors briefly describe their experience with phenylbutazone in the treatment of 26 cases of rheumatic fever seen at the Legouest Military Hospital, Metz, all the patients being soldiers of 20 years of age.

The drug was given intramuscularly in doses of 500 to 1,000 mg. daily during the first 3 to 6 days, this dosage being gradually reduced thereafter and the drug given by mouth as the general condition improved. Treatment was continued until the erythrocyte sedimentation rate had returned to normal or nearly so; this occurred on the average after about 3 weeks. No adverse side-effects were noted.

The authors comment on the rapid subsidence of articular pain, sometimes within a few hours of the first injection, and on the sense of well-being produced by the drug. The temperature usually fell rapidly during the first 24 hours of treatment. The erythrocyte sedimentation rate and blood fibrinogen level returned to normal in 2 to 3 weeks. In three cases with cardiac involvement the heart condition was restored to normal, but no specific action of the drug is claimed in view of the small number of cases. In no case was there involvement of the endocardium. All these cases would have been considered suitable for salicylate therapy [see following Abstract]. *H. F. Reichenfeld.*

Recent Series of 200 Cases of Acute Articular Rheumatism among Military Personnel. (Sur 200 cas récents de rhumatisme articulaire aigu observés en milieu militaire.) ABLARD, G., and LARCAN, A. (1954). *Presse méd.*, **62**, 1671. 23 refs.

The 3-year study reported here was carried out at the Metz Military Hospital, where 223 cases of acute rheumatism in 20-year-old recruits were treated, representing 5 per cent. of all admissions. The majority (114) of these young soldiers were experiencing their first attack of rheumatic fever. In 200 cases the attack (114 primary, 86 recurrent) was observed from its onset, the remainder being excluded from the study. Tonsillitis was observed in one-third of cases. The erythrocyte sedimentation rate (E.S.R.) was above 96 mm. in one hour in 56 cases, between 50 and 90 mm. in 54, and below 50 mm. in eighty. In general the course of the illness was benign, and the average period of hospitalization was 4 to 5 weeks. Transient, benign cardiac involvement was detected by electrocardiography in 49 cases, severe myocardial damage was noted in eight cases, valvular lesions of recent onset in fourteen, probable endocardial changes in eight, pericarditis in twelve, and a severe pancarditis in two.

Uncomplicated cases (168) were treated with salicylates by mouth in doses of 6 to 8 g. daily and this was increased and supplemented by intravenous administration if the E.S.R. exceeded 50 mm. in one hour. Penicillin was given in cases of tonsillitis. Hormone therapy was used in 28 cases with evidence of cardiac damage and in four uncomplicated cases which did not appear to react to salicylates, 200 mg. cortisone being given daily for 6 to 10 days and the dose reduced in succeeding weeks, the total dosage of cortisone being 3 to 5 g. Where ACTH (corticotrophin) was used the dosage was less than half that of cortisone. It is claimed that five patients with endocarditis recovered completely, while eleven were greatly improved; five appeared to derive no benefit.

While it is too early yet to assess the long-term effect of hormone treatment on rheumatic endocarditis, clinical impressions suggest that it represents a considerable advance on previous therapy. *David Preiskel.*

Rheumatic Crises provoked by Mitral Commissurotomy. (Les crises rhumatismales provoquées par la commissurotomie mitrale.) SOULIE, P., BOUVRAIN, Y., FORTIN, P., and CARAMANIAN, —. (1954). *Bull. Soc. méd. Hôp. Paris*, **70**, 879. 11 refs.

Out of a total of 120 cases of mitral stenosis treated by commissurotomy and followed up for periods of 6 months to 3 years, the operation was considered to have caused a recurrence of acute rheumatism in ten, which are here reported fully. In five cases there was no past history of rheumatic fever and in three cases the last attacks were 30, 13, and 6 years respectively before the operation. The two remaining patients had had attacks more recently (3 and 7 months respectively before operation). The flare-up followed the operation after an interval of 3 weeks to 2 months.

The authors feel that some of their findings are open to criticism for various reasons, but they conclude with some confidence that the operation should not be carried out in any case in which a recent rheumatic flare-up has occurred, as it is likely that a further relapse will be provoked. Although this will not necessarily prove to be of a severe type, they feel that the risk should never be incurred. *W. S. C. Copeman.*

Value of Blood Volume Determinations in the Study of Patients undergoing Surgery for Rheumatic Heart Disease. LIKOFF, W., BERKOWITZ, D., GEYER, S., STRAUSS, H., and REALE, A. (1955). *Amer. Heart J.*, **49**, 1. 1 fig., 8 refs.

In this study of the value of determination of the blood volume of patients undergoing surgery for rheumatic heart disease, carried out at Hahnemann Medical College and Hospital, Philadelphia, the blood volume was determined under fasting basal conditions in 100 such patients and 45 normal controls using radioactive-iodinated human serum albumin (R.I.S.A.) in accordance with the technique described by Storaasli and others (*Surg. Gynec. Obstet.*, 1950, **91**, 458). In analysing the post-operative results, morbidity was defined as congestive failure developing within 18 days after operation, and mortality as death due to cardiac causes, but excluding haemorrhage, embolism, and ventricular fibrillation directly attributable to the operation. The results were as follows (the estimated mean blood volume being given as ml. per kg. body weight):

45 normal subjects, 75·1;
54 patients without congestive failure, 73·9;
20 with failure responding to treatment, 100·3;
26 with failure not responding to treatment, 86.

Operation on the heart was performed in 59 patients in whom the blood volume was normal or nearly so. After operation two died and one developed congestive failure, a morbidity–mortality rate (MM) of 5·6 per cent. On the other hand, of 26 patients with raised blood volume, four died after operation and eleven developed congestive failure (MM 57·7 per cent.).

The results were also analysed according to the type of valvular lesion present.

(1) Of 28 patients with mitral stenosis and normal blood volume, one developed congestive failure (MM 3·5 per cent.), and of eight such patients with raised blood volume, five developed congestive failure (MM 62·5 per cent.).

(2) Of sixteen patients with aortic stenosis, none developed complications or died (MM *nil*).

(3) Of thirteen patients with combined mitral and aortic valvular disease and normal blood volume, two died (MM 15·4 per cent.), and of sixteen such patients with raised blood volume, two died and six developed congestive failure (MM 56·2 per cent.).

(4) One patient with mitral incompetence and raised blood volume died after operation.

In fifty (95 per cent.) of the 54 patients with chronic rheumatic heart disease who had not been in failure the blood volume was normal. However, in the remaining four the blood volume was raised and the postoperative morbidity–mortality was high. The reason for the increase in blood volume is uncertain, but it seems to indicate some change in cardiac physiology which interferes with postoperative progress. The authors consider that determination of the total blood volume serves as a useful guide in the selection of cases for surgery.

Arthur Willcox.

Evolution of Murmurs in Early Rheumatic Heart Disease. ZILLI, A., and GAMNA, G. (1954). *Amer. J. Med.*, **17**, 775. 5 figs, 11 refs.

At Mount Sinai Hospital (Chicago Medical School), Chicago, 41 patients between the ages of 2 and 15 years suffering from a first attack of rheumatic fever were studied for periods varying between several weeks and 3 years with special reference to the development of cardiac murmurs. For this purpose stethoscopic and logarithmic phonocardiograms were recorded over the apex, the mid-praecordium, and the pulmonary, aortic, and tricuspid areas. In most cases three recordings were made—in the acute phase, during recovery, and after stabilization—but the individual totals varied between two and eight. The patients fell into four groups:

(I) In twenty patients only systolic murmurs were detected at the first observation; these decreased or disappeared in about one-half of the cases, and increased in the remaining one-half. A basal systolic murmur caused by stenosis is characteristically represented by a diamond-shaped phonocardiographic tracing, and on this basis about one-third of the basal systolic murmurs found were considered to be transmitted from the apex. A pulmonary systolic murmur, not transmitted from the apex, was found in about one-half of the cases initially, but only in one-quarter at the final investigation; the majority of these murmurs are therefore attributed either to dynamic dilatation of the pulmonary artery or to rheumatic arteritis. By contrast, in about one-fifth of the cases an aortic, non-transmitted, systolic murmur remained present throughout, and was therefore interpreted as indicating organic aortic stenosis.

(II) In thirteen cases, all severe, a systolic murmur and a diastolic rumble were present at the first examination. In eight of these there was no longer any evidence of a diastolic rumble at the final examination, and in these cases the murmur is explained as due to relative mitral and tricuspid stenosis caused by ventricular dilatation or, in the absence of any demonstrable dilatation, as possibly due to oedema of the mitral leaflets.

(III) In four cases there was also an aortic diastolic murmur which persisted.

(IV) In four cases there were minimal systolic murmurs whose origin could not be localized. The results of this study emphasize the value of long-term observation.

Disappearance of a murmur suggests that it was originally functional in origin; this occurred in about one-half of the authors' cases of mitral systolic murmur and in about two-thirds of those in which a diastolic rumbling murmur was present initially; by contrast, aortic diastolic murmurs are seldom transient.

A. Schott.

Recent Experience in the Treatment of Rheumatic Carditis with Hormones and Salicylate. (Ulteriore contributo casistico sul trattamento ormonico-salicilico della cardite reumatica.) GELLI, G. (1954). *Minerva pediat.* (*Torino*), **6**, 951. 16 refs.

The beneficial effect of the combination of salicylates with cortisone or corticotrophin (ACTH) in the treatment of thirteen cases of rheumatic carditis has already been reported by Gelli and Meneghini (*Arch. ital. Pediat.*, 1953, **16**, 85). In the present paper the results in a further eleven cases are analysed, and the need for early and prolonged treatment is emphasized. Cortisone, which is probably preferable to ACTH because of the tendency to adrenal insufficiency in rheumatic fever, is given in doses of 50 mg. daily for a maximum of 3 weeks, the dose then being halved and the drug given for a further 30 to 60 days, after which the dose is halved again for a shorter period. In addition, 4 to 6 g. sodium salicylate is given daily, together with penicillin and streptomycin or aureomycin, while ascorbic acid and vitamins K and P are administered parenterally in large doses. A salt-free diet is advised, but no evidence of fluid retention or hypokalaemia was noted. No patient in this or in the previous series has relapsed. The response to this treatment is often dramatic and rapid, and signs of carditis disappear. It is thought probable that even endocardial damage may respond favourably, and the author regards this form of combined therapy as indispensable at the present time in cases of rheumatic fever.

A. Paton.

Group-A Beta-Haemolytic Streptococci and Rheumatic Fever in Miami, Fla. SASLAW, M. S., and STREITFELD, M. M. (1954). *Publ. Hlth Rep. (Wash.)*, **69**, 877. 15 refs.

Because of the reported low incidence of rheumatic heart disease, polyarthritis, and chorea and the lessened severity of these diseases in the warm, southern parts of the United States, the authors have investigated the incidence of Group-A β-haemolytic streptococci in the throats of 343 healthy children attending three schools in Miami, Florida. In most cases duplicate swabs were taken at monthly intervals between February and May, 1953, but in some more than two were taken, the average number for the whole group being 3·4. The children were selected to represent different racial groups and socio-economic levels. One swab was cultured on "difco" blood-agar base enriched with 4 per cent. defibrinated sheep's blood, and the others on various media in an attempt to assess the relative value of different media. Brewer's thioglycollate broth ("difco") and neopeptone heart-infusion agar difco containing 4 per cent. defibrinated sheep blood both proved valuable in recovering additional strains [but there is no evidence that such strains might not have been cultured from a second swab on the first medium]. Grouping and typing by the Lancefield precipitin method was performed, the latter for 36 types. In all, 59 strains of Group-A β-haemolytic streptococci were isolated from 47 children. All of the 27 typable strains were of Type 12 with one exception, which was Type 28. In 14 instances repeated cultures were positive. Of the 343 children observed over the 4 months' period 16·3 per cent. gave cultures of Group-A β-haemolytic streptococci; this compares with a figure of between 5 and 10 per cent. reported by Denny for normal children. No antistreptolysin-O titres were performed. There was no complete follow-up of all illnesses during the period of study, but none of the children were admitted to hospital for acute rheumatic fever or frank nephritis. *E. G. L. Bywaters.*

Rheumatic Fever and Rheumatic Heart Disease in Children as seen in Clinic Practice. I. Clinic Diagnostic Technique. DAVIS, L. L., and GREENE, M. H. (1954). *Amer. J. Dis. Child.*, **88**, 427. 32 refs.

The authors of this paper describe the work of the diagnostic rheumatic fever clinic at Meadowbrook Hospital, Long Island, New York, to which 306 children were referred by their family doctor during the school year 1951-52 for "evaluation of puzzling cardiac findings or questionable rheumatic symptomatology". The classic form of rheumatic fever is now less common than it used to be, and the "typical" case, in the authors' experience, is the child with a smouldering carditis and few, if any, of the orthodox criteria of rheumatism, presenting a formidable problem in diagnosis.

Great importance is attached at this clinic to the standardization of procedure in examination and in the recording of the results, the methods used being described in detail, and an attempt has been made to classify the findings which have proved most important and useful for the diagnosis of rheumatism in three categories, as follows:

1. *Positive evidence of rheumatic disease.* (*a*) Radiological signs of enlarged left atrium and left ventricle in the absence of congenital heart disease. (*b*) Systolic murmur of Grade 3 or greater intensity at the apex transmitted to the axilla. (*c*) Transient prolongation of A-V conduction in the presence of rheumatic-like symptoms indicates the presence of carditis. (*d*) Prolonged $Q–T_c$ similarly indicates the presence of carditis. (*e*) In the presence of cardiac findings of questionable significance, a history of rheumatic heart disease in both parents was considered to justify the diagnosis of "potential heart disease".

2. *Presumptive signs.* (*a*) Family history of rheumatic disease in a "sickly" child complaining mainly of abnormal fatiguability. (*b*) Changes in heart sounds or murmurs on repeated examination. (*c*) Choreiform movements or a history of chorea with minimal cardiac signs. (*d*) "Non-specific" electrocardiographic changes, such as notched P waves, in a child otherwise well. (*e*) A generally enlarged heart without alternative explanation.

3. *Helpful diagnostic characteristics.* (*a*) A report that the child is not well, though not definitely ill. (*b*) Marked depletion of vital capacity in an older child without respiratory disease. (*c*) Progressive pallor without a corresponding degree of anaemia. *M. MacGregor.*

Effects of Flying on Patients with Cardiovascular Disease. BOURNE, G. (1955). *Brit. med. J.*, **1**, 310. 3 figs, 2 refs.

Details are given of thirty patients with heart disease who have flown long distances without inconvenience or deleterious effects. The series includes cases of myocardial infarction, angina, hypertension, and severe rheumatic heart disease. In all cases the state of cardiac compensation was good, and adequate pressurization of the aircraft was assured as an essential preliminary.

[These findings confirm the view of most cardiologists that, provided the aircraft is pressurized, flying is as safe as any other method of transport for a patient with heart disease.] *C. W. C. Bain.*

Results of the Hormone Treatment of Rheumatic Fever. (Résultats du traitement hormonal de la maladie de Bouillaud.) MOZZICONACCI, P., and CARAMANIAN, M. K. (1955). *Arch. Mal. Cœur*, **48**, 3. 43 figs, bibl.

The authors give an account of the treatment with cortisone or corticotrophin (ACTH) of 267 children suffering from rheumatic fever. The maximum period of follow-up was 3 years. The cases were divided into three main groups:

(I) 23 patients with severe cardiac involvement and constitutional disturbances; of these seventeen recovered, twelve without recrudescence, and six died.

(II) 131 patients with simple carditis, some with choreic signs, of whom 114 recovered without recurrence up to the time of writing, and six died.

(III) 113 patients with acute articular rheumatism, and also in some cases chorea, of whom twelve suffered a

relapse, but 111 were eventually discharged without sign of cardiac involvement and two developed persisting murmurs; in 100 no recurrence has been reported.

Cortisone was used in the majority of cases, being given in doses ranging from 100 mg. per day, up to age 5, to 200 mg. per day for those aged 10 to 15 years, either orally or intramuscularly. ACTH was reserved for severe cases, such as those of pancarditis, heart failure, and the "malignant" type of the disease in which urgent measures were required and the intravenous route therefore justified, in doses of 10 mg. per day given by slow infusion. Treatment was given for 15 days and then, if the erythrocyte sedimentation rate (E.S.R.) was not below 20 mm. in one hour, was continued for further periods each of 15 days up to 4 to 6 weeks, with fortnightly reassessment, until the E.S.R. fell to below 20 mm. At this juncture the hormone was replaced by aspirin in a dose of 0·1 to 0·15 g. per kg. body weight until the E.S.R. became normal, when a progressively decreasing dose of hormone was given for 10 more days. In addition, 3 g. ammonium chloride was given daily along with the hormone. The use of heparin or ethyl biscoumacetate may have to be considered in cases of acute carditis, and in cases of cardiac failure the authors found it advisable to precede hormone therapy by digitalization for 24 to 48 hours. All patients were also given 1,000,000 units penicillin intramuscularly, followed by 400,000 units daily by mouth.

The authors regard hormone treatment as the most effective weapon against acute rheumatic fever, and while the treatment is not curative, it does appear to check recrudescence and to diminish the incidence of cardiac involvement in the articular type of the disease.

V. Reade.

Results of Hormone Treatment of Acute Rheumatism in Children. Comparison with Salicylate Treatment. (Résultats du traitement hormonal du rhumatisme articulaire aigu de l'enfant. Comparaison avec le traitement salicylé.) MARQUEZY, R. A., DI MATTEO, J., BACH, C., and SCHRUB, J. (1954). *Bull. Soc. méd. Hôp. Paris*, **70**, 844.

The authors compare the results of treatment with cortisone and ACTH (corticotrophin) in 85 cases of acute rheumatism in children, in which all the symptoms responded rapidly, with those in a series of 128 cases treated in classic fashion with salicylates in full dosage. After a very full discussion [which should be consulted in the original] they conclude that hormonal treatment is preferable for the acute articular stage of rheumatic fever and should last for 10 to 15 days. Longer periods are necessary only when the disease is unusually severe and the heart badly affected.

They consider that the therapeutic effect of hormones is good in so far as pericardial affection is concerned, but is uncertain when there is endocarditis and even more so when myocarditis is present. On the other hand they consider that the prophylactic effect of hormone therapy on all forms of rheumatic carditis is real and impressive.

W. S. C. Copeman.

Changing Status of Rheumatic Fever and Rheumatic Heart Disease in Children and Youth. WALLACE, H. M., and RICH, H. (1955). *Amer. J. Dis. Child.*, **89**, 7. 5 figs, 10 refs.

The authors have found few reports in the American literature which substantiate or refute the claim that there has been a change in recent years in the picture of rheumatic fever and rheumatic heart disease in children and young adults. In this paper they discuss the mortality of these two conditions as recorded in New York City over the 11-year period 1940-50 and the incidence of heart disease in children in the years 1943 and 1952.

In the period under review there was a significant reduction in the number of deaths from rheumatic heart disease in children and young adults under the age of 20, especially in white children. In 1952 as compared with 1943 fewer children had heart disease of rheumatic origin and it was noted that a higher proportion were placed in ordinary schools as opposed to special schools, indicating, presumably, freedom from cardiac disease. In the 11-year period 1940-50 there was a 74 per cent. decrease in mortality from rheumatic fever in the age group 0 to 20 years.

R. S. Illingworth.

Convalescence and Prophylaxis against Recurrence of Acute Articular Rheumatism in Children. (Convalescence et prophylaxie des crises de rhumatisme articulaire aigu chez l'enfant.) LABESSE, J., DAGONET, Y., POUJADE, L., and COURRAULT, R. (1955). *Arch. Mal. Cœur*, **48**, 94. 27 refs.

The authors first review the accepted evidence that acute articular rheumatism is a sequel of infection with *Streptococcus haemolyticus* Group A, usually of the throat or respiratory tract, and emphasize the infectivity and the familial tendency of the condition. During treatment the spread of infection and the risk of re-infection and superinfection (with another type of Group-A organism) must be combated, while during convalescence measures for prophylaxis and rehabilitation are essential.

Convalescence begins with the cessation of treatment with hormones and salicylates, and should be passed in a convalescent home to which the patient is sent directly from hôspital without spending any time in his own home. At the Hopital de La Roche-Guyon, which is a convalescent institution and is especially equipped for the reception of such cases, the condition of every child is assessed on admission and a swab of the throat taken, this being repeated weekly. The child is kept in bed until the temperature, pulse rate, and erythrocyte sedimentation rate (E.S.R.) are all normal and any cardiac condition has become stable. Prophylactic treatment is given daily throughout the stay, and is continued after discharge, in the form of sulphadiazine or penicillin, or both may be given in succession.

Any sign of reactivation of the disease is treated by return to strict bed rest, and aspirin is given in doses such as to produce a serum salicylate level of 30 to 35 mg. per 100 ml. In cases of re-infection, penicillin (1,200,000 units daily for 5 days, then 600,000 units daily for 5 days)

is used in preference to aureomycin. After discharge the parents are instructed as to the routine to be followed under medical supervision; the need for continuous protection with antibiotics is again stressed. After a quiescent period of 6 months, games may be permitted, unless a cardiac lesion is also present, when at least one year must elapse.

Among 49 children treated with 1 g. sulphadiazine daily for 6 weeks and followed up for 8 months there were two relapses (4 per cent.); in 100 patients given 200,000 units of penicillin orally twice a day there were six minor recurrences after 6 months (6 per cent.); and in twenty treated with sulphadiazine and then penicillin there was one case of relapse (5 per cent.). For comparison, among 131 children in whom treatment had lapsed there were 74 recurrences (56 per cent.) during a follow-up period of 11 months. Prophylaxis should continue until the age of 18, or possibly for life, in the case of associated cardiopathy. *V. Reade.*

Vessel Permeability in Juvenile Rheumatism. (Сосудистая проницаемость при ревматизме у детей.) SOKOLOVA-PONOMAREVA, O. D., and BISYARINA, V. P. (1954). *Pediatriya*, No. 6, pp. 17-21.

The plasma protein levels were studied at the Kalinin Medical Institute, Omsk, in ninety cases of active juvenile rheumatism, consisting of 38 cases of acute articular rheumatism, 32 of rheumatic carditis, and twenty of chorea. The average total plasma protein content was 3·02 per cent. lower than the normal value for the same age group; the plasma fibrinogen level was 2·35 per cent. higher in 51 cases and 1·57 per cent. lower in 34 cases; the plasma globulin level was 19·5 per cent. higher in 82 cases and lower than normal in only four cases; and the plasma albumin level was 20·3 per cent. lower than normal in 81 cases and higher in only five (in the remaining cases the values for all three plasma proteins were normal). In 79 cases the albumin : globulin ratio was significantly reduced. These changes are attributed to the changes in capillary permeability which occur in the active stage of acute rheumatism, as reported by the same authors, *Pediatriya*, No. 5, 1954, p. 3.

Analysis of the results showed that in cardiac and articular rheumatism, both in first and subsequent attacks, the plasma globulin content was increased and that of albumin decreased, signifying an increase in vascular permeability. In chorea the same was true in first attacks, but in subsequent attacks the changes were less in degree, signifying a less severe increase in capillary permeability. With clinical improvement the plasma protein pattern returned to normal in 26 out of the ninety cases, the total plasma protein content in the other 64 cases remaining lower than normal, although higher than before the institution of treatment. The plasma globulin level remained above normal in 56 cases and that of plasma albumin below normal in 63 cases.

It is concluded that the determination of the total and individual plasma protein levels in juvenile rheumatism is of value in judging the degree of activity of the disease process. *E. D. Fox.*

Fresh Air Treatment for Juvenile Rheumatism. (К вопросу об использовании открытого свежего воздуха при лечении ревматизма у детей.) GVELESIANI, K. G. (1954). *Pediatriya*, No. 6, pp. 41-45.

During a one-year period 133 children aged 10 to 15 years were admitted to the Children's Clinic of the Medical Institute of Tbilis (Tiflis), Georgian S.S.R., in the acute phase of various forms of rheumatism, the sex distribution being approximately equal. The patients were divided into two groups:

(A) 70 treated in the open air exposed to temperatures varying from −2·5° to 33·1° C.;

(B) 63 treated in normal wards.

The treatment in all cases included rest in bed, administration of salicylates (0·5 g. per year of age per day) and amidopyrine (0·1 g. per year of age per day), and a course of ten daily injections of 40 per cent. glucose solution containing 100 mg. of ascorbic acid. The average period of observation was 45 days.

It was found that in Group A the erythrocyte sedimentation rate and leucocyte count returned to normal sooner and that the rise in haemoglobin and the diuresis were greater than in Group B. In all cases the blood pressure was below normal initially; it had returned to normal on discharge in 76 per cent. of cases in Group A, and in only 46 per cent. in Group B. The results of treatment were classified as "significant improvement", "improvement", "no change", and "died". The proportion of cases in these categories were, respectively, 55 per cent., 43 per cent., and 2 per cent., and *nil* in Group A and 19 per cent., 75 per cent., 2 per cent, and 4 per cent. in Group B. There were relapses in 14 per cent. of Group B but in only 5·7 per cent. of Group A.

It is concluded that fresh air treatment, in conjunction with the more usual forms of therapy, should be used more widely for juvenile rheumatism. *E. D. Fox.*

Rheumatic-like Lesions in the Guinea-Pig: a Correlation of Toxic, Anaphylactogenic, Arthropathic, and Chemical Properties of Certain Crude Polysaccharides from *Klebsiella pneumoniae* Type B. JONES, R. S., CARTER, Y., and DE W. RANKIN, J. (1954). *Brit. J. exp. Path.*, **35**, 519. 7 figs, 20 refs.

In previous studies [not yet published] the two first-named authors found that certain mucopolysaccharides obtained from gastric mucin and a Friedlander type of organism produced lesions of the cardiac valves and joints on injection into guinea-pigs. In the investigations here reported from the University of Oregon Medical School, Portland, mucopolysaccharide fractions prepared from agar cultures of *Klebsiella pneumoniae* Type B were injected into guinea-pigs. Chemical analysis showed much variation in the protein nitrogen, hexosamine, and hexuronic acid content of different batches of the material used. Studies were made of the toxicity of these substances following intravenous injection, and of their ability to induce anaphylactic hypersensitivity by subcutaneous injection. [It is not possible from the description given to form a clear idea of how the experiments were carried out.]

Active anaphylaxis was induced in guinea-pigs by only

one of the fractions—an "acid-hydrolysis" fraction prepared by Wong's method (*Proc. Soc. exp. Biol. (N.Y.)*, 1938, **38**, 107 and 110), and this was also shown to be toxic. An "alkaline-hydrolysis" fraction was non-anaphylactigenic and less toxic. Daily injections of 2·5 or 5 mg. (intravenously or subcutaneously) of either fraction resulted in the development of cardiac valve lesions and synovial proliferative changes, with exudate, in certain joints, both reactions occurring within 1 to 14 days of the first injection. The authors regard the cardiac changes as non-specific and as part of a general inflammatory response in the guinea-pig, but consider that the changes in the joints are more specifically related to the injection of mucopolysaccharides. *E. J. Holborow.*

Pathogenesis of Rheumatic-like Lesions in the Guinea-Pig. JONES, R. S., and CARTER, Y. (1954). *Arch. Path. (Chicago)*, **58**, 613. 30 figs, 47 refs.

This study from the University of Oregon Medical School, Portland, is concerned with the changes produced in the cardiac valves and the joints of guinea-pigs by injection of various chemicals and organisms. Some of these produced proliferative changes, but the changes were not regarded as specific. The authors, while admitting that no specific thesis has been proved, hope that these experiments will widen the horizon for future investigation. *A. C. Lendrum.*

Diagnosis of Rheumatic Valvular Disease, 1924–1954. BRAMWELL, C. (1955). *Lancet*, **1**, 213. 4 figs, bibl.

Prevention of Acute Rheumatism. (La prévention du rhumatisme articulaire aigu.) RUTSTEIN, D. D. (1955). *Presse méd.*, **63**, 221.

Streptococcal Infection in a Family followed by Acute Rheumatism. (Streptococcie familiale avec maladie de Bouillaud.) GIRAUD, G., LATOUR, H., LEVY, A., PUECH, P., BONNET, H., BERTRAND, A., and ROUX, J. (1954). *Montpellier méd.*, **46**, 567.

Experimental Studies of the Biological Activity of Sodium Salicylate. (Ricerche sperimentali sull'attività biologica del salicilato di sodio.) SCHIAVETTI, L., and FERRARIS, F. (1955). *Reumatismo*, **7**, 70. 2 figs, 35 refs.

Localized Visceral Lesions in Rheumatic Fever. (Localisations viscérales particulières de la maladie de Bouillaud.) BESSON, F. (1955). *Praxis*, **44**, 133.

Local Oximetry of the Blood in Rheumatic Fever. (L'emossimetria distrettuale nella malattia reumatica.) SCALABRINO, R., and PASQUARIELLO, G. (1955). *Minerva med. (Torino)*, **1**, 445. 7 refs.

Prevention of Rheumatic Fever by the Use of Antibiotics. STOLLERMAN, G. H. (1955). *Bull. N.Y. Acad. Med.*, **31**, 165. 4 figs, 31 refs.

Differential Diagnosis of Rheumatic Fever in Office Practice. WEDUM, B. G., and RHODES, P. H. (1955). *J. Amer. med. Ass.*, **157**, 981.

Community Control of Rheumatic Fever. BUNN, W. H., and BENNETT, H. N. (1955). *J. Amer. med. Ass.*, **157**, 986. 14 refs.

On some Features of Rheumatic Fever and Rheumatic Heart Disease as seen in the National Cardiological Institute of Mexico. SALAZAR-MALLEN, M., and RULFO, J. (1955). *Ann. intern. Med.*, **42**, 607. 4 figs, 24 refs.

The Q-Tc, an Aid to the Diagnosis of Rheumatic Carditis. GULOTTA, G. A., PETERSON, W. L., and DANIELS, R. S. (1955). *U.S. armed Forces med. J.*, **6**, 162. 2 figs, 24 refs.

Chronic Articular Rheumatism
(Rheumatoid Arthritis)

Effect of Cortisone in the Long-Term Treatment of Rheumatoid Arthritis. Observation of 35 Patients over a 3-year Period. TOONE, E. C., and IRBY, R. (1955). *Amer. J. Med.*, **18**, 41. 3 figs, 21 refs.

The clinical course in 35 patients with rheumatoid arthritis who were given cortisone over a 3-year period is described in this paper from the Medical College of Virginia Hospitals, Richmond, Virginia. The ages of the patients (19 males and 16 females) ranged from 33 to 74 years. At the start of treatment the disease was classified as early in two cases only; in the majority it was advanced. The daily dosage of cortisone ranged from 50 to 150 mg. (average 75 mg.). The patients were treated in hospital at the beginning, the drug being given by intramuscular injection during this period. The immediate results were good in 34 cases. The long-term results, however, showed that none of the patients experienced complete remission of symptoms. At the end of 3 years only eleven patients had benefited sufficiently to continue taking cortisone, there being major improvement in seven and minor improvement in four. Of the remaining 24 patients in the series, nineteen ceased treatment because of toxic reactions or absence of any improvement in symptoms. There were five deaths, four attributable directly or indirectly to cortisone.

Toxic reactions, which were frequent and in ten cases were sufficiently severe to necessitate discontinuance of the drug, included moon-face, oedema, obesity, osteoporosis, and gastro-intestinal ulceration or haemorrhage. In six cases abscess of the buttock developed following the first injections. Severe psychosis was noted in three cases, and rapid progressive joint damage in two. Summarizing their results, the authors stress the fact that only eleven of the patients thought it worth while to continue cortisone for 3 years. They consider that the drug should be confined to those cases in which other forms of treatment have failed. *William Hughes.*

Hydrocortisone by the Oral Route in Rheumatoid Arthritis (Preliminary Clinical Study). (Hydrocortisone par voie buccale dans la polyarthrite chronique évolutive (étude clinique préliminaire).) LAYANI, F., and PEYRON, J. (1955). *Rev. Rhum.*, **22**, 30. 2 refs.

The authors record and discuss their observations in sixteen cases of rheumatoid arthritis treated with hydrocortisone free alcohol given orally; some of the patients were followed up for 6 months or more. The drug was given in an initial dose of 40 mg. daily, which was then

modified from week to week until the minimum daily dose sufficient to give reasonable relief was determined, this usually ranging from 30 to 60 mg. per day. The clinical effect was similar to that of cortisone, but comparable results were obtained with smaller doses. The most striking feature was the absence of any important side-effects. The authors confirm that hydrocortisone free alcohol is superior to cortisone in such cases.

Kenneth Stone.

Evaluation of Prolonged Cortisone Therapy in Rheumatoid Arthritis. A Four-year Study. BUNIM, J. J., ZIFF, M., and MCEWEN, C. (1955). *Amer. J. Med.*, **18**, 27. 7 figs, 11 refs.

The results obtained in 78 patients suffering from rheumatoid arthritis who were given cortisone for periods ranging from a few weeks to 4 years are reported from New York University College of Medicine. Of 71 patients treated for more than 6 weeks, sixteen were in remission, twenty showed major improvement, 31 minor improvement, and four were unimproved or worse. This group included 31 males and forty females, 35 of whom were over 50 and ten were under 20 years of age. Before treatment started arthritis has been present for 12 months or under in nineteen patients, for 1 to 10 years in 29, and over 10 years in 23. In seventeen patients the disease was in the early reversible stage and in about half it was in an advanced stage. The average daily dosage of cortisone in all except three cases ranged from 25 to 100 mg.; in three patients given more than 100 mg. a day peptic ulcer developed, and two perforated.

Analysing their results, the authors note that in thirteen of sixteen patients with remission the disease was in the reversible stage at the start of treatment. It was noteworthy that seven of the sixteen were between 10 and 29 years of age. In general, clinical improvement was paralleled by a fall in the erythrocyte sedimentation rate, but there were many exceptions. In the majority of patients subcutaneous nodules did not disappear during treatment, while in two patients new nodules developed for the first time. The most disconcerting objective finding was an increase in areas of bone destruction. Serial radiographs in twenty cases showed that areas of bone destruction were present in fourteen at the beginning of treatment; in eight of these the area increased, in five it was unchanged, and in one it was diminished. In the six cases in which there was no evidence of bone destruction before treatment osseous damage developed during administration of cortisone, although in five there was clinical and laboratory evidence of improvement. There were six deaths in the series, five of which were probably unrelated to cortisone therapy. The sixth patient died from a fulminating pneumococcal infection which was masked by cortisone. *William Hughes.*

Comparative Results of Treatment with Oral Hydrocortisone and with Cortisone. (Résultats thérapeutiques comparatifs de l'hydrocortisone buccale et de la cortisone.) DE SÈZE, S., DEBEYRE, N., and BORDIER, P. (1955). *Rev. Rhum.*, **22**, 38. 10 refs.

The hydrocortisone acetate suspension given by injection for its local effect is but feebly soluble in water and body fluids, whereas the recently introduced oral preparation, hydrocortisone free alcohol, is some 35 times more soluble in serum. In this study the authors compare the results achieved with oral hydrocortisone in the treatment of 31 patients with rheumatoid arthritis and two with ankylosing spondylitis, all of whom had previously been treated for periods varying from 4 months to 3 years with maintenance doses of cortisone. Initially the oral hydrocortisone was given in approximately the same dosage as cortisone. The progress of the patients was then reviewed at intervals of a fortnight, when the daily dose was reduced by 10 mg. at a time until signs of relapse appeared.

In only two cases was little or no change noted on substituting hydrocortisone, the other patients being definitely better than when under treatment with cortisone; improvement in some cases was rapid and spectacular. In all but one of 26 patients a raised erythrocyte sedimentation rate fell, in nine cases to normal, on changing to oral hydrocortisone.

It was found that with 40 to 50 mg. hydrocortisone the clinical and biological response was just superior to that with 75 mg. cortisone—in other words, that hydrocortisone is 1½ times as active as cortisone. All the patients in this study had tolerated maintenance doses of cortisone without side-effects, but after the change to oral hydrocortisone three patients developed tachycardia and swelling of the face. Previous reports on the incidence of side-effects with oral hydrocortisone have been conflicting, Boland reporting a diminution or disappearance of such side-effects as oedema and "moon-face", whereas West and Newns (*Lancet*, 1954, **2**, 168) found quite the opposite. *Kenneth Stone.*

Failure of Skin Testing to detect Antigen-Antibody Properties in the Tissues of Rheumatoid Arthritis. LANSBURY, J., ALLEN, G. E., and ROGERS, F. B. (1955). *Amer. J. med. Sci.*, **229**, 191. 2 refs.

The authors report on reactions to intradermal injections of test material derived from joint fluid, joint synovium and rheumatoid nodule of three patients with typical rheumatoid arthritis. The three test materials and a control material derived from *E. coli* filtrate were administered to a series of twenty cases of rheumatoid arthritis and a series of twenty non-rheumatic control patients. All cases gave a moderate response to the bacterial filtrate. None gave any local or systemic response to the filtrates of rheumatoid tissue. It is concluded that those features of rheumatoid arthritis which suggest antigen-antibody reaction may lie in the field of some as yet unknown immune mechanism.—[*Authors' summary.*]

Rheumatoid Affections of the Skin. (Afecciones cutaneas reumatoides. Comentarios a nuestra casuistica.) VILANOVA, X., PIÑOL, J., and ROTÉS-QUEROL, J. (1954). *Act. dermo-sifiliogr. (Madr.)*, **46**, 106. 1 fig.

The authors discuss 166 cases in which there were both cutaneous and rheumatoid manifestations, occurring among patients seen at the University Dermatological Clinic, Barcelona. They are considered in two groups,

those of primary rheumatoid disease with an accompanying cutaneous syndrome, and those of a rheumatoid syndrome occurring in association with disorders of the skin. The series included seventeen cases of lupus erythematosus with articular involvement in nine, fifteen cases of scleroderma with articular involvement in four, twelve cases of erythema nodosum with arthralgia or articular swelling in all, and 69 cases of psoriasis arthropathica. *Eric Dunlop.*

Free Erythrocyte Porphyrin and Plasma Copper in Rheumatoid Disease. [In English.] JEFFREY, M. R., and WATSON, D. (1954). *Acta haemat.* (*Basel*), **12**, 169. 2 figs, 14 refs.

The anaemia of rheumatoid arthritis is similar in many respects to the anaemia of sepsis. As it has been shown that in the latter the concentration of free erythrocyte protoporphyrin and serum copper is raised, the authors, in a study here reported from the Royal National Hospital for Rheumatic Diseases, Bath, determined the levels of these substances in the heparinized venous blood of fasting control subjects and patients with rheumatoid arthritis, using for the former determination the method of Grinstein and Watson (*J. biol. Chem.*, 1943, **147**, 675) and for the latter the method of Watson. The plasma iron content was also estimated.

In twenty normal subjects the mean value of free erythrocyte porphyrin (essentially protoporphyrin) was 21·5 μg. (maximum 44 μg.) per 100 ml. erythrocytes. In uncomplicated cases of rheumatoid arthritis (excluding those with conditions producing iron deficiency) this value was within the upper limit of normal (taken as 60 μg. per 100 ml.) in two-thirds of the cases, but was above it in nine out of twenty men, and in five out of thirty women. There was a high negative correlation with haemoglobin value ($r = -0{\cdot}49$) and with plasma iron content ($r = -0{\cdot}68$ in men, $-0{\cdot}46$ in women), but no significant correlation with age or with duration or activity of the illness. After treatment with iron (given intravenously as saccharated iron oxide three times weekly for 3 months) the porphyrin value, where it had been abnormally high, returned to normal.

The average plasma copper concentration was 101 μg. per 100 ml. for twenty normal men and 106 μg. for twenty normal women, the upper limits of normal being taken as 120 and 135 μg. per 100 ml. respectively. Of the patients with rheumatoid arthritis, 25 out of 35 men and 52 out of 65 women gave results above the normal range, with means of 144 μg. and 159 μg. per 100 ml. respectively. There was a negative correlation between plasma copper levels and haemoglobin values ($r = -0{\cdot}70$ and $-0{\cdot}55$ for men and women respectively), and also between plasma iron concentration and copper content ($r = -0{\cdot}76$ and $-0{\cdot}54$ respectively). After treatment with gold salts (given intramuscularly as calcium aurothiomalate over about 5 months to a total of 1 g. of the metal), plasma copper values did not change significantly in 18 cases despite a mean rise in the haemoglobin value of 1 g. per 100 ml.; in response to intravenous iron therapy, high copper levels increased somewhat and remained high despite correction of the anaemia. The authors conclude that the raised porphyrin values observed were due to iron deficiency rather than to the rheumatoid arthritis; but the hypercupraemia observed is only partly explained by the presence of anaemia and could, they suggest, be due to decreased utilization of copper in consequence of the impaired formation of haemoglobin and erythrocytes thought to be present in rheumatoid anaemia. *E. G. L. Bywaters.*

Ocular Signs of Still's Disease. (Les manifestations oculaires de la maladie de Still.) FRANÇOIS, J., and HAUSTRATE, L. (1954). *Bull. Soc. belge Ophtal.*, No. 107, 383. 1 fig., 89 refs; (1954). *Ann. Oculist.* (*Paris*), **187**, 1061. 1 fig., 89 refs.

The authors report a case in a 2-year-old boy with bilateral insidious and chronic iridocyclitis, band-shaped corneal opacity, and complicated cataract. This triad is pathognomonic of infantile rheumatism, although it is not possible to say if it belongs to a chronic progressive rheumatism or to Still's disease. In every case, even in the absence of acute articular lesions, it is indicative of rheumatism in the child. *L. Coppez.*

Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis. Antirheumatic Potency, Metabolic Effects, and Hormonal Properties. BUNIM, J. J., PECHET, M. M., and BOLLET, A. J. (1955). *J. Amer. med. Ass.*, **157**, 311. 7 figs, 4 refs.

Metacortandralone and metacortandracin, two new synthetic steroids, were tried in the treatment of seven patients with rheumatoid arthritis, in all of whom conventional treatment had been unsuccessful and in four there had been no response to cortisone. The investigation was concerned mainly with metacortandralone, the authors stating that metacortandracin appeared to be very similar in action and potency.

Metacortandralone was given by mouth in an initial suppressive daily dose of 30 to 60 mg.; this was later reduced to a maintenance dose varying from 5 to 25 mg. daily. None of the patients was aware of the change in treatment from salicylates or cortisone to metacortandralone. Subjective improvement was noted within 4 to 6 hours of administration of the first dose of metacortandralone and was obvious within 24 hours; objective improvement was more gradual, being maximum after 2 to 3 weeks. There was consistent improvement in joint inflammation, indicating that the drug possessed antirheumatic properties, and this was confirmed in three patients by histological examination of biopsy specimens of the synovial membrane taken before and during treatment, a striking subsidence of inflammation being noted. Side-effects were not serious, and disappeared when the dose was reduced to maintenance level. In two patients signs and symptoms of arthritis returned within about 2 weeks of withdrawal of the drug; no other constitutional symptoms were noted. In the four cases in which there had been no response to cortisone the maintenance dose of metacortandralone appeared to be from one-third to one-fifth of that of cortisone, but this estimate may require revision after more experience.

Administration of metacortandralone resulted in a

prompt and uniform fall in the eosinophil count and a reduction in the urinary excretion of 17-ketosteroids. A rise in the serum cholesterol level was observed in six cases. Carbohydrate metabolism appeared to be unaffected, and no change was observed in the sodium or potassium balance with a dose of 30 mg. daily; 50 mg. daily was necessary to induce a negative nitrogen balance.

The authors conclude that these synthetic steroids are several times more potent than cortisone, and that this potency does not appear to be accompanied by an increase in the severity of side-effects. They emphasize, however, that a long-term investigation is necessary to determine their true value. *B. E. W. Mace.*

Clinical Trial of a Derivative of a Bile Salt in the Treatment of Rheumatoid Arthritis. A Preliminary Communication. HIGHTON, T. C. (1954). *N.Z. med. J.*, **53**, 569. 1 fig., 11 refs.

After drawing attention to the clinical observation that an attack of infective hepatitis may induce a remission of rheumatoid arthritis, the author recalls the successful results obtained by Hench with intravenous injections of bile salts. At the Queen Elizabeth Hospital, Rotorua, 56 patients with rheumatoid arthritis were given an intramuscular injection of 200 mg. sodium triketocholanic acid, a bile-salt derivative, twice a week. To counteract the irritant effect of the injection an equal volume of 2 per cent. procaine was added to the bile-salt preparation; this, however, was omitted from the injections given to patients known to be hypersensitive to procaine. Few side-effects were observed. Injection abscesses developed in some cases, and a sensation of premenstrual tension was experienced by a number of patients when the injection was administered during the pre-ovulatory phase. Other side-effects were polyuria and pain in the right hypochondrium.

Injection of this bile-salt preparation produced no immediate dramatic effect, but in 36 patients improvement was observed about the third to the sixth weeks, and was progressive thereafter, except for attacks of "arthritis in miniature". Improvement was maintained for periods varying between 18 months and 3 years, but the authors consider that the course of injections must be continued for at least 2 years. They believe that the results compare favourably with those obtained with ACTH and cortisone. *A. Garland.*

Auto-antibodies in Rheumatoid Arthritis. A Simple Method of Demonstration with Possible Diagnostic Application. (Autoanticuerpos en la poliartritis crónica progresiva. Método sencillo de demostración con posibles aplicaciones diagnósticas.) FOZ, A., BATALLA, E., and ESPACIO, L. (1954). *Rev. Diagn. biol.* (*Madr.*), **3**, 460. 6 refs.

The similarity between the Coombs test for incomplete antibodies and the Waaler–Rose test for rheumatoid arthritis suggests that the rheumatoid-arthritis serum (R.A.S.) factor may be an auto-antibody against the patient's own globulin. The erythrocytes act passively as a carrier of the globulin and can be replaced by other carriers, such as erythrocytes of other species. In studies carried out at the Municipal Hospital for Infectious Diseases, Barcelona, the authors have used a system of *Brucella abortus* sensitized with human incomplete anti-*Brucella* antibody for detection of the R.A.S. factor. The human anti-*Brucella* serum had an agglutinin titre of 1 in 15 and an incomplete antibody titre of 1 in 2,500. A washed, killed suspension of *Br. abortus* was sensitized by incubation for one hour at 37° C. with this serum diluted to a titre of 1 in 125. In performing the test the patient's serum is diluted with saline in successively doubled dilutions in ten tubes, 0·5 ml. of each dilution is added to 0·5 ml. sensitized *Brucella* suspension, and the mixture incubated at 37° C. Agglutination is judged visually. A control series of dilutions is set up, using a suspension of unsensitized *Br. abortus*. If the test serum contains *Brucella* antibodies, they are removed by absorption.

The test was carried out on 54 healthy control subjects and 23 patients with rheumatoid arthritis. In nineteen of the latter, antibody titres ranged from 1 in 80 to 1 in 10,240; in one case the titre was 1 in 40, in another the test result was doubtful, and in two cases it was negative. Only one of the 54 control subjects gave a positive test result (titre 1 in 320). The Waaler–Rose test was negative in five of the cases of rheumatoid arthritis. The authors report that they are using with success a system of Rh-positive erythrocytes sensitized with incomplete Rh-antibodies [but give no details].

M. Lubran.

Observations on 69 Cases of Rheumatoid Arthritis treated with Di-(2-chloroethyl)-methylamine Hydrochloride. (Quelques considérations sur 69 cas de polyarthrite chronique evolutive traités par le chlorhydrate de méthyl-bis-β-chloroéthyl-amine.) ROBECCHI, A., CARTESEGNA, F., and DANEO, V. (1954). *Rev. Rhum.*, **21**, 823.

At the Rheumatological Centre, Turin, 69 patients (20 men and 49 women), of whom 62 had rheumatoid arthritis and five "psoriatic rheumatism", were given a dose of 5 mg. nitrogen mustard intravenously either on alternate days or every third day; after four injections there was an interval of 8 to 20 days and then another four injections completed the course. In the rheumatoid arthritic patients the results were "excellent" in 19 per cent., "satisfactory" in 47·5 per cent., "insignificant" in 17·5 per cent., and there was no benefit in 16 per cent. Neither sex nor age appeared to influence the results, and if the first course of treatment failed no benefit was derived by repeating it. The cases of psoriatic rheumatism reacted in much the same way as the rheumatoid patients in as far as the joint condition was concerned, and the skin lesions cleared in one case. But treatment had to be interrupted in four of the five cases because of persistent vomiting. In the group of patients with rheumatoid arthritis, however, side-effects were few.

[In most of these cases the treatment was followed by a standard course of gold or cortisone; it is therefore difficult to assess the long-term effects of the nitrogen mustard. Nevertheless, the authors claim that one patient with rheumatoid arthritis who reacted very well

to a course of nitrogen mustard was still in "satisfactory condition" one year later, having, in the intervening period, been maintained on 37·5 mg. cortisone daily.]
David Preiskel.

A Study of Gamma Globulin in Rheumatoid Arthritis. VAUGHAN, J. H., ARMATO, A., GOLDTHWAIT, J. C., BRACHMAN, P., FAVOUR, C. B., and BAYLES, T. B. (1955). *J. clin. Invest.*, **34**, 75. 4 figs, 18 refs.

In a study carried out at Harvard University Medical School, Boston, of the fate of serum proteins in patients with rheumatoid arthritis small groups of such patients and normal control subjects were given intravenous injections of gamma globulin and albumin derived from both rheumatoid arthritic and normal blood and labelled with radioactive iodine (^{131}I), its rate of disappearance from the blood stream being then observed. The elimination of both globulin and albumin was found to be more rapid in the rheumatoid patients, irrespective of the origin of the protein fraction, but otherwise the two groups showed little difference. In further experiments *in vitro* it was shown that both rheumatoid and normal joint tissues removed at operation took up labelled gamma globulin without any significant differences. From these and other experiments the authors conclude that there is no evidence to support the concept of a specific relationship between joint tissue and plasma gamma globulin in rheumatoid arthritis. *Harry Coke.*

Rheumatoid Purpura treated with ACTH, Cortisone, and "4560 RP". (A Series of Five Cases.) (Purpura rhumatoïde [ACTH, cortisone, 4560 RP]) (à propos de 5 observations.) LANGERON, L., FRUCHART, G., DESTOMBES, A., and LEMAIRE, E. (1954). *Bull. Soc. méd. Hôp. Paris*, **70**, 917. 1 ref.

Rheumatoid purpura, or Schönlein–Henoch's disease, is characterized by a cutaneous purpuric eruption, abdominal and renal symptoms, and a generalized arthralgia and oedema. The authors present five cases in which the administration of ACTH or cortisone, and in some cases "4560 RP", resulted in marked improvement or cure. The authors regard the condition as a consequence of irritation of the sympathetic nervous system, and emphasize the value of skin biopsy in diagnosis. *Kate Maunsell.*

Treatment of Rheumatoid Arthritis with Minimal Doses of ACTH. (Tratamiento de la artritis reumatica con dosis minimas de ACTH.) SITZERMAN, B. (1955). *Rev. argent. Reum.*, **19**, 212. 15 refs.

Orthopaedic Management of Rheumatoid Arthritis. PETTY, H. (1955). *Physiotherapy*, **41**, 69.

Aetiology and Pathogenesis of Rheumatoid Arthritis. DRESNER, E. (1955). *Amer. J. Med.*, **18**, 74. Bibliography.

Management of Rheumatoid Arthritis in Relation to Physical and Surgical Measures. PEABODY, C. W. (1955). *J. Mich. med. Soc.*, **54**, 317. 5 figs.

Unusual Manifestations of Rheumatoid Nodules. Report of Three Cases. MIKKELSEN, W. M., DUFF, I. F., and ROBINSON, W. D. (1955). *J. Mich. med. Soc.*, 54, 292. 5 figs, 14 refs.

(Osteo-Arthritis)

Cheilotomy and Multiple Perforations in the Treatment of Osteo-Arthritis. (Cheilotomie e perforazioni multiple nella cura della artrosi deformante.) BARBIERI, M. (1954). *Minerva chir. (Torino)*, **9**, 981. 34 figs, 31 refs.

The treatment of twelve patients with stiff and painful joints by cheilotomy combined with multiple drilling of the joint surface is reported from the Orthopaedic Clinic of the University of Genoa. In six cases the knee was affected, the joints involved in the remaining cases being the elbow, hip, and ankle. The author reviews the results in this small series (the follow-up period being 1 to 4 years in seven of the twelve cases) and claims that in 90 per cent. the results were good, although in no cases were all the essential features of the condition—pain, limitation of movement, and instability—eliminated, while in some of the cases these symptoms were aggravated by the operation.

[The arthritic changes shown in the radiographs reproduced are not of comparable origin or nature, nor do the photographic illustrations permit the reader to judge for himself whether or not there has been an increase in the range of movement. The claims made for this method in the treatment of osteo-arthritis are not admissible on the evidence provided by a small series of heterogeneous cases, nor are they borne out by the follow-up details given.] *L. Michaelis.*

Osteo-Arthritis Deformans of the Luschka Joints. CAVE, A. J. E., GRIFFITHS, J. D., and WHITELEY, M. M. (1955). *Lancet*, **1**, 176. 4 figs, 12 refs.

The authors, discussing the possible causes of cervicobrachial neuritis, state their belief that protrusion of the cervical intervertebral disks is less frequently responsible than deforming osteo-arthritis of the neurocentral joints of Luschka. They base this opinion on their findings in an anatomical study of 60 adult cervical spines carried out at St. Bartholomew's Hospital Medical College, London, and describe twelve unselected cases of cervicobrachial neuritis in out-patients attending the hospital, in all of whom they demonstrated the condition radiologically. The suggested mechanism is a compression angulation of the contents of the intervertebral canals by bony encroachment into their medial end.
A. C. Lendrum.

Osteo-Arthritis of the Hip. LLOYD-ROBERTS, G. C. (1955). *J. Bone Jt Surg.*, **37B**, 8. 64 figs, 97 refs.

This paper deals, firstly, with an attempt to relate symptoms to the morbid anatomical and radiographic appearances of the osteo-arthritic hip, and, secondly, discusses the factors that predispose to its development.

The author considers that the capsule is the principal articular structure from which pain arises. Studies of

this structure in the hip joints of 25 patients who had undergone operation, showed that synovial congestion and subsynovial fibrosis are constant features, and that, these appear to be due to articular debris from the degenerate joint surfaces. This debris tends to accumulate in the synovial pocket below the neck of the femur, and the resultant capsular fibrosis and thickening is the cause of many of the signs and symptoms of this disease. The morbid anatomical changes are discussed in detail.

The aetiological aspects are discussed under four main headings. Incongruity between the joint surfaces of the hip is a recognized cause of osteo-arthritis; in the author's series of 124 hips, adolescent coxa vara was the commonest cause (eight cases), and the mechanism of production of arthritis in this condition is discussed in detail. Congenital dysplasia, meaning a developmental abnormality of the femoral head or neck, or of the acetabulum, tending to subluxation, is another common cause (26 cases out of 124). Methods of determining minor degrees of dysplasia of this sort are discussed, and the importance of early and vigorous treatment for congenital subluxation of the joint is emphasized by a series of radiographs.

The hypothesis that osteo-arthritis of the hip may be the result of ischaemic change in the head is considered, but little direct evidence in favour of this can be found.

No aetiological cause could be found in 73 of the 124 hips studied. It was noted that both bilateral and unilateral disease occurs more commonly in women, and that bilateral disease is the more commonly associated with osteo-arthritis in other joints; arthritis of this kind may have a "constitutional" rather than a local cause.

The author concludes by pointing out that cartilage degeneration most commonly occurs with advancing age, and that osteo-arthritis is merely an acceleration of this process; a better understanding of normal cartilage metabolism may help to solve the problem of osteo-arthritis. *B. E. W. Mace.*

Development and Nature of Osteo-Arthritis of the Hip Joint. PRIDIE, K. H. (1955). *Rheumatism*, **11**, 2. 9 figs.

(Spondylitis)

Acrylic Arthroplasty in Ankylosing Spondylitis. (L'arthroplastie acrylique dans la spondylarthrite ankylosante.) D'AUBIGNE, R. M., RAMADIER, J. O., and POSTEL, M. (1955). *Rev. Rhum.*, **22**, 16. 3 figs.

The authors review the results of operations designed to increase the mobility of hip-joints ankylosed as a result of extension of ankylosing spondylitis. They urge (with justification) that in patients with a combination of ankyloses of the spine, hip, and often also one or both knees, any effort made to restore some degree of movement at least to the hip- and knee-joints is worth while, since without such attempts the patients are for all practical purposes helpless, having the choice of only two positions, the horizontal and the upright; they cannot change position without assistance, cannot sit, and can usually walk only with extreme difficulty with crutches.

The authors have so far performed arthroplasty on 38 occasions in 21 patients, but the results in only fourteen who were subjected to bilateral operation are discussed here. In seventeen operations the Judet-type of prosthesis was employed, but the best results were obtained with the use of a special type of acrylic prosthesis for the head and neck of the femur which has a long intramedullary stem. In thirteen of the fourteen patients increased mobility of the hip-joints, ranging from 36 to 43 degrees, was achieved, all thirteen could walk more easily, and twelve could sit down unaided; three of the patients have been able to resume their former employment. The special hazard of the operation is hyperaemia, which makes good haemostasis difficult. The extensive changes which occur in the soft-parts round the joints, such as deposit of fat and matting of the fascial planes in every layer, are described. The authors believe that preoperative exercise of the legs carried out in bed may prevent these changes, a crucial feature in these cases, from developing fully. In four cases they tried excision of the head and neck of the femur without fitting a prosthesis, but the results were less satisfactory.

L. Michaelis.

X-Ray Treatment of Ankylosing Spondylitis. HILTON, G. (1955). *Rheumatism*, **77**, 10. 4 figs, 1 ref.

Writing from University College Hospital, London, the author states that the treatment of ankylosing spondylitis by immobilization or physiotherapy alone has proved of only temporary value, therapy with vaccines and gold has failed, and cortisone, while useful in an acute phase, has not proved curative. Radiotherapy, however, has changed the whole outlook. The earlier the treatment—preferably when still only the sacro-iliac joints are involved—the better the results. Misdiagnosis of an abnormal radiological picture, for example, one of osteitis condensans ilii, is a possible cause of failure.

In the acute phase, when there is general illness, complete rest is indicated and irradiation at this stage is contraindicated. Later, however, even advanced cases can be benefited by localized radiation. It is important to consider the dosage received by the gonads. In the male the dose to the testes, if adequately protected, is negligible (about 5 *r*), and libido is not affected by such a dose, although it is often impaired by the general effects of the disease; sperm counts made before and after treatment have shown no reduction in numbers. In the female, however, the situation is very different and it is impossible completely to avoid affecting the ovaries. A direct sacro-iliac field will give an ovarian dose of 400 to 500 *r*; this will always cause amenorrhoea, which may be permanent in women approaching the menopause, and may last 8 to 12 months in younger women. A later pregnancy may produce a normal child, and genetic damage may not show itself until the second or even third generation; hence some authorities advise a full sterilizing dose of irradiation in all female cases. In the author's view irradiation should be given to younger women only when there are definite radiological changes or physical incapacity. Before beginning treat-

ment septic foci and anaemia should be dealt with. The haemoglobin level does not usually fall during treatment, and may even rise. The number of leucocytes should be checked by making weekly counts, treatment being suspended if the count falls. A radiograph of the chest should be taken routinely, for irradiation can stir up a latent focus of tuberculosis.

The aim of treatment in spondylitis is quite different from that in cancer therapy and much smaller doses are needed; the beneficial effects are probably due to depression of cell activity, increased blood and lymph flow, diapedesis, and proliferation of fibroblasts. In technique, wide-field *x*-ray "baths" have been generally abandoned, and irradiation is now given to the sacro-iliac joints plus the lumbar spine or whole spine—preferably the whole spine, to lessen the chances of recurrence—200 to 250 kV being used for the spine and large joints, and 120 to 150 kV for small joints and muscle attachments. Three spinal fields 8 cm. wide and 15 to 20 cm. long are used. In the male the sacro-iliac joints are treated by one transverse field, but in the female each side is treated by separate tangential fields in order to minimize dosage to the ovaries. There is no general agreement on optimum dosage; a usual course is a total surface dose of 1,500 to 2,000 *r*, 300 *r* being given to one field or 200 *r* to 2 fields daily and the whole treatment spread over one month. For peripheral joints a total of 1,000 *r* is delivered to the centre of the joint over 2 weeks. Physiotherapy, consisting first of passive and then of active movement, should be given concurrently, and breathing exercises to improve chest expansion are most important. Surgery, such as osteotomy of the hip-joint or spine, is of very little value and may entail the risk of causing increased ossification, while manipulation only aggravates the condition.

The results of treatment depend largely on the stage of the disease at which irradiation is begun. In early cases in which only the sacro-iliac joints are involved signs and symptoms may disappear in 100 per cent. of cases. In moderately advanced cases this can be expected in about 70 per cent., but even bedridden patients can be greatly helped and become useful citizens. Involvement of the hip-joints causes the most crippling disablement and has the worst prognosis. Complete relief of pain may take 1 to 3 months to achieve. There is no close correlation between the erythrocyte sedimentation rate (E.S.R.) and activity of the disease; a fall in the E.S.R. may lag months behind clinical improvement, and treatment policy should therefore be guided primarily by symptoms. In such a chronic disease it is difficult to say whether cures can be permanent, since the data are as yet inadequate, but the author has known cases in which the progress of the disease was halted for 10 to 15 years. Recurrences may be due to incomplete spinal treatment, unsuitable occupation or exposure, or severe illness of other sorts. Treatment has little influence on the radiological picture, and calcification or ossification usually remains unchanged. Rehabilitation, after-care, and the choice of work are most important; both heavy manual work and a wholly sedentary occupation are to be avoided. *J. Walter.*

Anatomy, Physiology, and Radiology of the Sacro-iliac Joints. (Anatomie, physiologie et radiologie des articulations sacro-iliaques.) QUEROL, J. R. (1954). *Rhumatologie*, **6**, 277. 9 figs, 4 refs.

Diagnosis of Disorders of the Sacro-iliac Joints. (Diagnostic des affections des articulations sacro-iliaques.) ARLET, J. (1954). *Rhumatologie*, **6**, 285. 2 figs.

Infective Sacro-iliac Arthritis. (Les arthrites sacro-iliaques infectieuses.) SERRE, H. (1954). *Rhumatologie*, **6**, 292. 3 figs.

(Miscellaneous)

Effect of Periarticular Procaine Infiltration on Joint Temperature. FLETCHER, E., JACOBS, J. H., and ROSE, F. C. (1954). *Ann. phys. Med.*, **2**, 123. 5 refs.

The temperature within a joint before and after procaine infiltration was recorded in patients with and without arthritic disease at the Royal Free Hospital, London. The medial or lateral aspect of the periarticular tissues of the knee were infiltrated with 5 ml. 2 per cent. procaine and the temperature within the joint measured by means of an indwelling thermocouple in a 1-millimetre needle. A rise of several degrees occurred within 30 minutes in all the joints observed, the rise being highest when the initial temperature was low. In a second experiment the thermocouple needle was withdrawn after the initial temperature had been read and reinserted later after intervals varying from 30 minutes to 15 hours. The results were similar to those obtained in the first experiment, but it was observed that in one instance the rise in temperature was maintained for 15 hours. No changes in temperature were observed when the thermocouple was introduced into the joint without previous injection of procaine or normal saline. The mean intra-articular temperature was raised in cases of osteo-arthritis and it is suggested that this may be due to increased vascularity of the joint.

The authors consider that the rise in intra-articular temperature which follows periarticular infiltration of procaine is the result of local paralysis of vasoconstrictor nerve endings, this allowing vasodilatation of the vessels supplying the synovium and capsule; and that the "partial success attending various intra-articular injections" for the relief of pain in chronic joint disease is due to the preliminary procaine analgesia. *J. B. Millard.*

Physiotherapy in Degenerative Rheumatism. (Physiothérapie du rhumatisme dégénératif.) MARCHAND, J. H., CLAUTOUR, J., and DESPROGES-GOTTERON, R. (1955). *Rev. Rhum.*, **22**, 45.

The authors discuss the physical treatment of degenerative joint disease, particularly cervical spondylosis with brachial neuralgia. Their first line of attack is *x*-ray therapy, which they consider to have an anti-inflammatory action and to be superior to any other form of treatment. The dosage, which should not exceed a total skin dose of 1,200 to 1,500 *r* spread over 3 or 4 weeks, is small enough to be free from any undesirable effects. The first dose, usually one of 100 *r*, provokes a temporary exacerbation of pain, coming on some 3 to

5 hours after irradiation and lasting about 2 hours. If this reaction is not excessive a second dose of 150 *r* is given 48 hours later, successive doses being at this level. In many cases this treatment is followed by complete and rapid relief and for some patients two or three treatments may suffice. In other cases the pain abates gradually during the month after treatment.

When pain persists beyond this period the authors have recourse to the use of constant current, calcium ionization being employed for its sedative effect. For cervical stiffness persisting after pain has abated they use iodine ionization, the current being applied transversely through the neck. Examples of other types of arthrosis are discussed from the same point of view. Their treatment of sciatica follows the same general plan. They have found that relief of pain follows *x*-ray therapy in cases of osteo-arthritis of the hip and knee and in subacromial bursitis. *Kenneth Stone.*

Periarteritis Nodosa: Recognition and Clinical Symptoms. BLANKENHORN, M. A., and KNOWLES, H. C. (1954). *Ann. intern. Med.*, **41**, 887. 6 refs.

On the basis of the pathological findings, 45 cases of necrotizing angiitis occurring at the Cincinnati General Hospital (University of Cincinnati) were divided into three groups:

(1) In 21 cases the condition was designated "secondary" periarteritis nodosa and was found after a careful search in patients dying of hypertensive renal disease.

(2) In fourteen cases the typical Kussmaul–Maier type of periarteritis nodosa was present, in which the small and medium-sized arteries were involved and the lesions were situated at the points of branching, particularly in muscle. Lesions of various ages were found together and the condition was associated with vascular obstruction and hypertension. All organs in the body were commonly involved.

(3) The remaining ten were regarded as cases of hypersensitivity angiitis. Here the arterioles, venules, capillaries, and small arteries of the viscera and interstitial tissues were involved. All lesions appeared to be of the same age and showed an exudative reaction. Hypersensitivity angiitis was commonly associated with visceral interstitial inflammation, necrotizing glomerulonephritis, and fibrinoid pneumonia.

Clinically, eosinophilia was common in the cases of periarteritis nodosa and rare in those of hypersensitivity angiitis. Uraemia, rare in primary periarteritis, was common in hypersensitivity angiitis. In the cases studied primary periarteritis nodosa ran a long clinical course, whereas hypersensitivity angiitis was a fulminating disease with fever, skin rash, nephritis, and myocarditis, and there was a frequent history of exposure to some antigenic substance. It is concluded that primary periarteritis nodosa and hypersensitivity angiitis represent two distinct conditions. *C. Bruce Perry.*

Scleroderma (Based on a Study of Over 150 Cases). LEINWAND, I., DURYEE, A. W., and RICHTER, M. N. (1954). *Ann. intern. Med.*, **41**, 1003. 19 figs, bibl.

In this paper from New York University Post-Graduate Medical School and the University Hospital, New York, the clinical features and pathology of scleroderma as observed in 150 cases seen over a period of 14 years are discussed. In 25 cases the disease was of the circumscribed type, but in the remainder there was evidence of generalized systemic involvement. The ratio of females to males was 2·7 : 1. After a brief account of the clinical signs and symptoms and the laboratory findings, the authors describe the clinical and pathological aspects of the disease system by system. The results of laboratory tests were not diagnostic of or specific to scleroderma; the erythrocyte sedimentation rate was raised in 85 per cent. of the cases; calcium metabolism was normal, and in some cases abnormal findings suggested focal involvement of certain viscera.

The authors describe at length the changes which occur in the lungs, heart, kidneys, gastro-intestinal tract, and blood vessels. In general they consist in changes in collagen, changes in the arteries (acute arteritis), and the immediate and remote effects of collagen degeneration and arterial obstruction upon the skin and viscera. [This section of the paper is, however, too detailed for abstraction and should be studied in the original.] The aetiology of scleroderma and the pathogenesis of the calcinosis which is observed in some cases are discussed. After a brief reference to the various drugs already tried in treating this disease the authors describe their experience with cortisone in eight cases, in all of which some improvement was observed.

[It is surprising that in such a long and detailed account no reference is made to the papers of Cullinan and Harper (*Proc. roy. Soc. Med.*, 1953, **46**, 507 and 512), in which the sigmoidoscopic and radiological changes in the colon are described. Only brief mention is made of the changes in the jejunum and ileum which Abrams, Carnes, and Eaton (*Arch. intern. Med.*, 1954, **94**, 61) have shown may dominate the clinical picture and lead to premature death from malabsorption.] *Nigel Compston.*

Treatment of Chronic Arthritis by the Intra-articular Injection of a Plastic Material. Experimental and Clinical Details. (Essai de traitement des arthrites chroniques par injection intra-articulaire de matière plastique. Données expérimentales et cliniques.) ARNULF, G., BENICHOUX, P., and MORIN, G. (1954). *Mém. Acad. Chir.* (*Paris*), **80**, 933. 3 figs, 1 ref.

The authors conceived the idea of treating chronic arthritic joints by the intra-articular injection of a syrupy solution of an inert synthetic resin which, it was hoped, by spreading over the eroded articular surface and solidifying, would provide as it were a new "cartilage". After a large number of experiments an acrylic resin, a polymer of methylmetacrylate, allied to that used in the Judet arthroplasty ("plexiglas") was found to be the most suitable, and a non-toxic solvent was found in the monochlorhydrin of glycol.

Experiments were conducted on forty animals (22 dogs and 18 rabbits). Both hip-joints were exposed, and from each femoral head a fragment of cartilage and underlying bone was gouged out. Then on one side only—the other being left untreated as a control—a few drops of the sterilized acrylic solution was introduced

into the joint space. This formed a thin pellicle on the articular surface, filling in the traumatized zone. The animals were killed at intervals varying from one month to one year. On examination of the hip-joints the difference on the two sides was striking: on the side treated with the resin there was a perfectly regular surface, the experimental lesion being smoothly covered over; on the control side the injured zone was roughly eroded.

These experiments having shown that this plastic material was well tolerated and had a favourable effect on cicatrization of a traumatic lesion, and having regard to the proved inert nature of the acrylic head used in the Judet operation, the authors have employed the treatment in a few cases of osteo-arthritis of the hip-joint in man. The small number of cases and the short period of follow-up preclude definite conclusions at this juncture, but pain in each case was suppressed for several months. The future will show if this "chemical arthroplasty" has a place in the treatment of suitable joint conditions.

Kenneth Stone.

Diagnostic Significance of Pulmonary Hypertrophic Osteo-Arthropathy. VOGL, A., BLUMENFELD, S., and GUTNER, L. B. (1955). *Amer. J. Med.*, **18**, 51. 20 figs, bibl.

From the Metropolitan Hospital, New York, seven cases of pulmonary hypertrophic osteo-arthropathy associated with pulmonary disease are reported, in six of which there was bronchial carcinoma and in one a lung abscess. The classical features of pulmonary hypertrophic osteo-arthropathy were present in all cases—namely, bone pain, stiffness of the fingers, muscle weakness, broadened finger ends, and redness and warmth of the overlying skin, the bone tenderness improving after removal of the underlying cause. In five of the seven cases the presenting symptoms were referable to the extremities, and in some the appearances strongly suggested rheumatoid arthritis. In one case the bone changes did not give rise to symptoms. The authors consider that pulmonary hypertrophic osteo-arthropathy is the outcome of a sustained increase in arterial flow with capillary stasis, caused by some pathological intrathoracic reflex. They state that there is no reported case of pulmonary hypertrophic osteo-arthropathy due to uncomplicated pulmonary tuberculosis, and therefore the presence of clubbing in a case of doubtful aetiology would favour a diagnosis of carcinoma rather than of pulmonary tuberculosis. A careful search for pulmonary hypertrophic osteo-arthropathy, including radiological examination, should be made in any case of lung disease where the diagnosis is in doubt. *A. Gordon Beckett.*

Contribution to Therapy with the New Antirheumatic Drug "Osadrin" (formerly "K317"). (Ein Beitrag zur Therapie mit dem neuen Antirheumatikum "Osadrin" (bisher "K317").) HUSSEL, W. (1955). *Medizinische*, **9**, 329.

Certain Aspects of Disordered Muscular Metabolism in Rheumatic Joint Diseases. (Alcuni aspetti del dismetabolismo muscolare nell'artrite reumatoide.) SCOPINARO, D., RIVANO, R., and SOLARI, S. (1955). *Reumatismo*, **7**, 65. 12 refs.

Arthrosis and Somatotrophic Hormone. (Artrosi e ormone somatotropo.) LUCHERINI, T., CECCHI, E., and SCHIAVETTI, L. (1954). *R.C. Ist. sup. Sanita*, **17**, 1067. 34 figs, 46 refs.

Rehabilitation of the Chronic Arthritic Hand. NEWMAN, M. K., GOLDSTEIN, A. S., WALL, P., and JEWETT, H. B. (1955). *J. Mich. med. Soc.*, **54**, 313. 7 refs.

Rehabilitation in Arthritis. A Case Report. JACKSON, W. M., SIGLER, J. W., ENSIGN, D. C., FLEMING, J. L., and LONG, C. (1955). *J. Mich. med. Soc.*, **54**, 330.

Arthritis and Injury. DURMAN, D. C. (1955). *J. Mich. med. Soc.*, **54**, 301. 4 figs, 1 ref.

Disk Syndrome

Use of Traction in Backache. FRAZER, E. H. (1954). *Med. J. Aust.*, **2**, 694. 3 figs, 18 refs.

There are many causes of low backache, the most frequently encountered being physical and/or emotional trauma. The end-result of most lesions is muscle tension, and to counteract this spinal traction is valuable. A vertical traction appliance is described in which use is made of the patient's body weight, and the resistance due to friction when a traction table is used is avoided. It is claimed that almost every joint in the body may be stretched by this method. The appliance consists of a self-locking hoist fixed to a wall, the hoist being connected by a wire over a ceiling pulley to a steel cross-bar. A spring balance is incorporated in the traction wire. The patient is suspended from the cross-bar by a special, well-padded corset, which fits round the thorax. A leather gaiter fixed to each leg or a pelvic band is attached to a steel bar fastened to the floor. By this method traction up to 400 lb. (181 kg.) is given for about 5 minutes, the traction being applied gradually and increased at each session. The author claims good results in 80 to 90 per cent. of cases which failed to respond to other methods of treatment, and he quotes the results obtained with traction at various centres in Europe, the percentage of "good results" at six centres averaging 69·8. He advocates administration of sedatives, such as bromide, as a routine and mephenesin 10 minutes before traction is applied. All patients are examined clinically and radiologically before treatment is started, but care should be exercised in patients with peptic ulcer, high blood pressure, hernia, cardiac disturbances, or gross haemorrhoids. *J. B. Millard.*

New Approach to the Treatment of Cervical Osteo-Arthritis with Radiculitis. FOWLKS, E. W. (1954). *Arch. phys. Med.*, **35**, 765. 2 figs, 11 refs.

In this paper from the Veterans Administration Hospital, Portland, Oregon, the pathological anatomy of the cervical vertebrae, including the atlanto-axoid and the occipito-atlantoid articulations, is first discussed. It is then pointed out that the presenting symptom of cervical osteo-arthritis is often referred pain leading in some instances to misdiagnosis of the condition.

From a wide experience of the treatment of cases of cervical osteo-arthritis the author found that simple traction often induced considerable muscle spasm and was not, therefore, always successful. Electromyographic tracings showed that moist heat tended to reduce this spasm, and a combination of moist heat (in a cabinet) and traction was found to be a more effective therapeutic measure. In about 20 per cent. of over 300 cases some restriction of movement was still present after treatment, and for this the author used manipulation, the technique of which is described. *B. E. W. Mace.*

General Pathology

Thorn's Test Prolonged over 24 Hours. (Le test de Thorn prolongé sur 24 heures.) DE GENNES, L., MATHIEU DE FOSSEY, B., BRICAIRE, H., GUILLON, J., and DELTOUR, G. (1954). *Ann. Endocr.* (*Paris*), **15**, 653. 7 figs, 8 refs.

In Thorn's original test for estimating the efficiency of the adrenal cortex counts of the eosinophil granulocytes made immediately before and 4 hours after the injection of 25 mg. ACTH are compared, a fall of less than 50 per cent. in the number being taken to indicate adrenal insufficiency. It later became clear, however, that more prolonged adrenal stimulation was needed for reliability, and Thorn himself proposed extension to 48 hours, during which a total of 95 mg. ACTH would be given.

In this paper from the Hôpital Broussais, Paris, the authors describe in detail their own modification, in which the test is prolonged to 24 hours, 25 mg. ACTH being injected every 6 hours—the first injection at 8 a.m., the last at 2 a.m.—making a total dose of 100 mg. Eosinophil counts are made immediately before and at 4 hours and 24 hours after the first injection and 24-hour specimens of urine are collected from the day preceding to the day following the test for estimation of 17-keto- and 11-oxysteroids. The results of the test are:

(1) Normal (positive): if the mean fall in the 4-hour and 24-hour eosinophil counts exceeds 50 per cent., and the daily excretion of 17-ketosteroids is increased by more than 3 mg. (normal 12 to 18 mg. for men, 7 to 10 mg. for women) and that of 11-oxysteroids by more than 20 μg. (normal 30 to 50 μg.).

(2) Doubtful: if the mean eosinophil count falls by 30 to 50 per cent., and 17-ketosteroid and 11-oxysteroid excretion increase by less than 3 mg. and 20 μg.

(3) Pathological (negative): if the mean eosinophil count falls by less than 30 per cent., and there is no increase in 17-ketosteroid or 11-oxysteroid excretion. In normal subjects the results are normal at both 4 and 24 hours, and prolonging the test merely shows that the adrenal response persists under the influence of ACTH. Examination of 52 cases of Addison's disease showed that results were uniformly in accord with the clinical diagnosis; a normal result must be considered as strong evidence against the diagnosis. In all but two of the cases a very low value for the daily 17-ketosteroid excretion was obtained; after administration of ACTH the figure in general remained low, but in two cases it became normal, and this part of the test is not therefore considered a reliable criterion of adrenal insufficiency. Determination of 11-oxysteroid excretion gave much more consistent results.

The Thorn test reveals many instances of adrenocortical insufficiency apart from that occurring in Addison's disease. In a study of 24 cases of non-Addisonian asthenia with pigmentation of the skin—a picture suggestive of Addison's disease but differing in its clinical course—prolongation of the test to 24 hours showed its increased diagnostic value. Thus, in some of these cases the result was pathological at 4 hours but normal at 24 hours, indicating that the adrenal cortex responded normally to more effective stimulation; in other cases the result of the classic test was normal, but the response at 24 hours pathological, indicating an adrenal cortex incapable of responding to prolonged stimulation. In various other endocrinological conditions, such as myxoedema and pituitary affections, pathological results of the test were recorded in many cases, and similar indication of adrenal insufficiency was found in two cases of chronic diarrhoea, while in six cases of haemochromatosis the prolonged test was negative in all at 24 hours, although in a few it had been normal at 4 hours.

In conclusion, the authors urge that in order to avoid false pathological results the 24-hour test is essential. Discussing the different elements of the test, they consider the amount of the daily 17-ketosteroid excretion to be an unreliable guide, but the eosinophil count is reliable as is the determination of 11-oxysteroid excretion, and this last, they suggest, should become routine practice. *Kenneth Stone.*

Aminotripeptidase Content of Synovial Fluid in Arthritic Diseases. ZIFF, M., SIMSON, J., SCULL, E., SMITH, A., SHATTON, J., and MAINLAND, D. (1955). *J. clin. Invest.*, **34**, 27. 3 figs, 10 refs.

The enzyme aminotripeptidase is widely distributed in the tissues, being especially richly concentrated in the leucocytes. In inflammatory reactions in a fluid-containing body space, such as the synovium, it might be expected that the amount of enzyme released by the dissolution of inflammatory cells and those of the lining membrane would be correlated with the degree of inflammation. On the basis of this theory the authors have measured the enzyme activity in articular fluid by the rate of hydrolysis of glycylglycylglycine in a "veronal" buffer at *p*H 7·8 and a temperature of 37° C., cell-free and unhaemolysed synovial fluid being obtained by centrifugation at 3,000 r.p.m. The activity was expressed as the percentage hydrolysis of substrate per hour.

At New York University–Bellevue Medical Center, examination of 112 specimens of fluid from the knee-joints of 98 patients gave the following ranges. In eleven cases of degenerative joint disease it ranged from 1·4 to 6·9 per cent.; in seventeen cases of acute rheumatic fever from 3·6 to 12·2 per cent.; in 31 of rheumatoid arthritis from 3·3 to 56·3 per cent.; in five of gonococcal arthritis from 5·7 to 13·0 per cent.; and in sixteen of gout from 3·3 to 46·2 per cent. Widely scattered and

relatively high values were a feature of the findings in rheumatoid arthritis and to a lesser extent in gout. Statistical analysis showed a positive correlation between enzyme level and duration of symptoms, and a highly significant difference in the mean enzyme levels of the six groups. [In a small group of miscellaneous diseases only a maximum figure of 42 per cent. is given.]

In degenerative joint disease and in rheumatic fever the level of aminotripeptidase in the serum was little different from that in the synovial fluid, but in cases of rheumatoid arthritis and gout the synovial levels ranged far in excess of that in the serum. There was only slight correlation between the leucocyte count and the enzyme level. It is pointed out that determination of the synovial enzyme level as a measure of the severity of the inflammation and as a means of differentiation of various types of joint disease shows good agreement with the results obtained by a study of the characteristics of the synovial fluid by other means, although admittedly some overlapping occurs. It is suggested therefore that, provided the duration of the condition is taken into account, determination of the enzyme level in the synovial fluid should be of some value in differential diagnosis. The lack of correlation with the leucocyte count suggests that the source of the enzyme is more closely associated with an extrusion or degradation of the synovial lining cells.

Harry Coke.

Erythrocyte Sedimentation in the First Quarter of an Hour in Rheumatic Fever. A More Sensitive Test. (La sédimentation globulaire du premier quart d'heure au cours de la maladie de Bouillaud. Sa plus grande sensibilité.) JOSSERAND, A., and GERMAIN, D. (1954). *Lyon méd.*, **192**, 321. 6 refs.

The authors have determined the erythrocyte sedimentation rate (E.S.R.) in ten cases of acute rheumatic fever, using the Cordier–Chaix vertical-tube technique but taking the reading after the first quarter of an hour as well as at one hour. Results showed that while the patients were febrile erythrocyte sedimentation was very rapid during the first quarter of an hour of the test, but when body temperature fell and during convalescence observation of the E.S.R. for one hour was generally necessary to show abnormality. The authors conclude that during acute rheumatic fever the degree of erythrocyte sedimentation at the end of 15 minutes gives a better indication of the acuteness of the inflammatory process than does the reading of the E.S.R. at the end of an hour, although the latter may be a better measure of the general state of the patient. *Kathleen M. Lawther.*

Determination of Anomalous Viscosity in Pathological Joint Fluids. SUNBLAD, L. (1954). *Scand. J. clin. Lab. Invest.*, **6**, 288. 2 figs, 13 refs.

The author, working at Södersjukhuset, Stockholm, describes a method for determining the degree of anomalous viscosity in synovial fluid. [The original paper must be studied for technical details.] While the degree of correlation between anomalous and intrinsic viscosity was fairly high at a chosen stress, the presence of even a small fraction of highly polymerized hyaluronic acid caused marked anomalies in flow, whereas the intrinsic viscosity was less affected. The author therefore suggests that determination of anomalous viscosity is of more value than determination of intrinsic viscosity for detecting the presence of highly polymerized fractions of hyaluronic acid in pathological fluids—*e.g.*, fluids which occur in rheumatoid arthritis after treatment with hydrocortisone (*Scand. J. clin. Lab. Invest.*, 1354, 6, 295).

Since no quantitative estimation of hyaluronic acid is required the method could thus be used as a clinical test for degradation of hyaluronic acid in pathological fluids. The author also suggests that the determination of anomalous viscosity may be of value in studying hyaluronic-acid changes when other mucopolysaccharides are present—for example, in connective-tissue extracts. *J. Warwick Buckler.*

Histology of Lupus Erythematosus. ELLIS, F. A., and BUNDICK, W. R. (1954). *Arch. Derm. Syph. (Chicago)*, **70**, 311. 3 figs, 7 refs.

From a review of the literature it does not appear to be agreed that chronic discoid lupus erythematosus can be differentiated from disseminated acute or subacute lupus erythematosus on histological examination of biopsy material from a skin lesion. In a series of 213 cases of lupus erythematosus (acute in 25, subacute in 25, and chronic in 163) the authors found an excellent correlation between the histological appearances and the clinical diagnosis. The histological features which were of most value in the differential diagnosis were: atrophy of the epidermis with severe oedema (seen in the acute form of the disease) and epidermal thickening, acanthosis, plugging, and infiltration (seen in the chronic form). In the subacute form the histological appearances were similar to those of the acute form except that there was less oedema. The authors were unable, however, to establish an absolute distinction between the three phases.

(One of the contributors to the discussion of this paper described a case of long-standing discoid lupus erythematosus, in which death was due to an unrelated cause and necropsy revealed lesions in the spleen which were typical of systemic lupus erythematosus. Still another contributor referred to the development in some cases of both chronic discoid and acute lupus erythematosus of a delicate line or zone of fibrinoid degeneration along the epidermal basement membrane.) *Bernard Lennox.*

Effects of 17-Hydroxycorticosterone (Compound F) on Human Eosinophils. HUDSON, B. (1954). *Aust. J. exp. Biol. med. Sci.*, **32**, 601. 14 refs.

Blood was incubated with different concentrations of compound F for 4 to 6 hours at 38° C. No significant changes were detected in the number of eosinophils in blood rendered incoagulable either by heparin or defibrination. No morphologic changes were detected in the eosinophils. The results of these experiments do not support the hypothesis that eosinolysis is responsible for the phenomenon of hormone induced eosinopenia.—[*Author's summary.*]

Contribution to the Study of the Relation between Erythrocyte Sedimentation and Focal Infection in Rheumatism. (Contributo allo studio delle correlazioni fra sedimentazione globulare e infezioni focali reumatiche.) MAFFEI, G. (1954). *Ateneo parmense*, **25**, 349. 5 figs, 46 refs.

Characteristics of the Fibroplastic System. III. Histogenesis of Rheumatic Lesions. (Caracterización del sistema fibroblastico. III. Histogenesis de las lesiones reumáticas.) COSTERO, I., BARROSO-MOGUEL, R., and CHEVÉZ, A. (1954). *Arch. Inst. Cardiol. Med.*, **24**, 437. 8 figs, 12 refs.

Modifications of Capillary Permeability in Rheumatism treated with Sodium Salicylate. (Modificazioni della permeabilità capillare in reumatici trattati con salicilato di sodio.) SCALABRINO, R., and PASQUARIELLO, G. (1955). *Minerva med. (Torino)*, **1**, 446. 4 figs, 32 refs.

Serological Reactions in Acute Rheumatism. Estimation of Antistreptolysin. (Reactions sérologiques dans le rhumatisme aigu. Dosage des antistreptolysines.) STADTSBAEDER, S., and DE SOMER, P. (1955). *Brux.-méd.*, **35**, 434. 9 refs.

A Histochemical Study of the Lymphadenopathy of Rheumatoid Arthritis. (Étude histochimique des adénopathies de la polyarthrite chronique évolutive.) JUSTIN-BESANÇON, L., RUBENS-DUVAL, A., VILLIAUMEY, J., and CAROIT, M. (1955). *Rev. Rhum.*, **22**, 10. 3 figs, 7 refs.

Serum Protein Fractions and the *p*H of the Blood in Rheumatism. (Über Serumeiweissfraktionen und den *p*H-Wert im Blut bei Rheumatikern.) KUKOWKA, A. (1955). *Z. Rheumaforsch.*, **14**, 24. 22 refs.

New Serum Turbidity Test with Mercuric Chloride in Rheumatoid Arthritis. (Su un nuovo test al sublimato nell'artrite reumatoide.) BACCARINI, V., and GOSPODINOFF, A. (1955). *Reumatismo*, 7, 98. 35 refs.

ACTH, Cortisone, and Other Steroids

Treatment of Tuberculous Sero-Fibrinous Pleurisy with ACTH. (Le traitement des pleurésies séro-fibrineuses tuberculeuses par l'A.C.T.H.) SORS, C., and TROCME, Y. (1954). *Rev. Tuberc. (Paris)*, **18**, 167. 14 refs.

The authors report seven cases of tuberculous pleural effusion treated with ACTH (corticotrophin) at the Hôpital Laënnec, Paris. Detailed case histories are given. In four cases the effusion was acute and of short duration, in two it was subacute or chronic, and in one it developed after the induction of pneumothorax.

ACTH was given slowly over 8½ hours daily as an intravenous infusion in 250 ml. glucose-saline for periods up to 14 days, along with 1 g. streptomycin, and in some cases 250 mg. isoniazid. The dose of ACTH in the earlier cases was 20 mg. daily, but experience showed that this could be reduced to 10 mg. daily. The authors emphasize the importance of slow administration, stating that the slower the infusion, the greater the effect of ACTH and the smaller the dose required.

The results were dramatic, ACTH producing rapid absorption of the effusion and return of the temperature to normal levels. No serious side-effects were observed.

T. M. Pollock.

Long-Term Control of Severe Bronchial Asthma with Oral Cortisone. SAVIDGE, R. S., and BROCKBANK, W. (1954). *Lancet*, **2**, 889. 5 figs, 7 refs.

The results obtained with cortisone in the treatment of thirteen cases of severe bronchial asthma of at least two years' duration are described in this paper from Manchester Royal Infirmary. The dose of cortisone, which was given by mouth, did not exceed 100 mg. daily, and the duration of treatment was 7 to 80 weeks. In six cases there was great improvement; for example, one patient, formerly bedfast, was able to lead a life of limited activity, while another, who had repeatedly lost time from work, experienced a relapse on one occasion only during a year's treatment, when a blank solution was substituted for the cortisone. Improvement, mostly subjective, was noted in four other patients. Of the remaining three patients, two died while receiving cortisone (see next Abstract), and one, who failed to show any improvement, died from bronchopneumonia 7 months after the course of cortisone was completed. The commonest side-effect was gain in weight. A moderate rise in blood pressure was noted in three patients, while in three others there were episodes of pneumonitis during treatment which responded to administration of an antibiotic. Most of the patients had a relapse within a short time of the cessation of treatment.

R. S. Bruce-Pearson.

Two Deaths during Cortisone Treatment of Bronchial Asthma. SAVIDGE, R. S., and BROCKBANK, W. (1954). *Lancet*, **2**, 893. 2 figs, 10 refs.

In a previous paper [see preceding Abstract] the authors reported two deaths from chronic asthma during cortisone treatment; in the present paper they describe these two cases in detail. The first patient, a man aged 45 with 20 years' history of bronchitis, developed asthma which did not respond to the usual methods of treatment. At first symptoms were relieved by cortisone, but later there were repeated relapses, although he was receiving a maintenance dose of 12·5 to 75 mg. daily. He died in status asthmaticus after 5 months' treatment while receiving a dose of 75 mg. daily. The second patient, a man aged 29, had had asthma almost continuously for 3 years. Improvement followed administration of cortisone, although the patient was not entirely free from spasm. He was later readmitted to hospital and died in status asthmaticus, the maintenance dose at the time of death being 75 mg. daily.

The authors consider that suppression of spontaneous adrenal activity by cortisone therapy might have been partly responsible for death in these two cases. They cite eight similar cases from the literature, and conclude that "cortisone treatment is dangerous to life in some undefined types of asthma".

[Though this conclusion may be correct, no evidence in support of it is provided by these two cases. Both patients had severe asthma, and death appears to have been the result of the disease.] *R. S. Bruce-Pearson.*

Landry–Guillain–Barré Syndrome: Cardiovascular Complications. Treatment with ACTH and Cortisone. CLARKE, E., BAYLISS, R. I. S., and COOPER, R. (1954). *Brit. med. J.*, **2**, 1504. 2 figs, bibl.

After briefly reviewing earlier papers containing references to cardiovascular complications of the Landry–Guillain–Barré syndrome the authors describe 3 cases of the syndrome seen at Hammersmith Hospital, London, in each of which there was circulatory collapse with hypotension. The first patient, a woman aged 63, died 6 days after admission, but post-mortem examination showed no abnormality of the myocardium apart from some hypertrophy due to pre-existing hypertension. In the second case, in a man of 45, there were hyperkalaemia and hyponatraemia possibly due to acute adrenal insufficiency; in this case both the nervous and cardiovascular symptoms improved promptly when cortisone and digoxin were administered. The third patient, a man aged 30, was admitted complaining of back pain, headache, and stiffness of the neck. Weakness of the muscles developed rapidly and it became necessary to aid respiration. In this case the cardiovascular collapse was accompanied by a pericardial friction rub and a recrudescence of the muscle weakness.

The symptoms and treatment of these cases are discussed. In the authors' opinion the circulatory collapse is due to myocardial involvement and not to loss of peripheral vascular tone. They suggest that treatment should include infusion of noradrenaline to combat the hypotension, together with digoxin and cortisone in the hope that these may improve the myocardial function and perhaps favourably influence the pathological process. *L. G. Kiloh.*

Action of Hydrocortisone on the Hyaluronic Acid of Joint Fluids in Rheumatoid Arthritis. SUNDBLAD, L., EGELIUS, N., and JONSSON, E. (1954). *Scand. J. clin. Lab. Invest.*, **6**, 295. 2 figs, 21 refs.

At the Södersjukhus, Stockholm, the synovial fluid from the knee-joints of fourteen patients with active rheumatoid arthritis was examined before and 2 to 3 days after the intra-articular injection of 50 mg. of hydrocortisone acetate. The joints were not emptied completely, but the degree of effusion was calculated by a dilution method.

It was found that the beneficial local effect of intra-articular injection of hydrocortisone was always accompanied by biochemical changes in the joint fluid, and that the converse applied in a few cases in which "butazolidin" (phenylbutazone) or a synthetic hyaluronidase-inhibitor was similarly administered. There was a rise in hyaluronic acid concentration in the majority of cases, but the most consistent change was an increase in the degree of polymerization of hyaluronic acid, as manifested by a rise in both the intrinsic viscosity and the degree of anomaly of flow; in about half the cases the intrinsic viscosity rose to normal. In a few cases in which repeated aspiration was carried out, the maximum response occurred after 2 to 4 days. The volume of the effusion decreased from an average of 20 ml. to an average of 4 ml.

A slight but significant decrease in hyaluronidase-inhibitor activity of the fluids was observed after intra-articular administration of hydrocortisone, and the authors therefore suggest that the changes in the hyaluronic acid cannot be ascribed to inhibited depolymerization. In their view, the hormone probably acts directly or indirectly on the synovial tissue, where the hyaluronic acid is presumably synthesized.

J. Warwick Buckler.

Approach to the Prediction of Diabetes Mellitus by Modification of the Glucose Tolerance Test with Cortisone. FAJANS, S. S., and CONN, J. W. (1954). *Diabetes*, **3**, 296. 6 figs, 13 refs.

Present methods of assessing carbohydrate tolerance may not be sufficiently sensitive to reveal the prediabetic state which is not infrequently present in the apparently healthy relatives of persons with diabetes. The authors, working at the University of Michigan Medical School, Ann Arbor, have therefore devised a modification of the glucose tolerance test in which cortisone is used to unmask any latent diabetic tendency. After a preliminary investigation to determine the dose of cortisone which was large enough to reveal any impairment of carbohydrate tolerance already present without impairing the tolerance of a healthy control subject, a trial was carried out on:

(1) Fifty healthy subjects who had no recent family history of diabetes,
(2) 152 apparently healthy relatives of diabetic patients.

The two groups were comparable in respect of age and sex distribution. Each subject was given a standard diet containing 300 g. of carbohydrate for 3 days and a standard glucose tolerance test was then carried out on two successive days, 50 mg. cortisone being given by mouth 8½ and again 2½ hours before the second test. (Heavier patients were given 62·5 mg. cortisone at the same time intervals.)

A diabetic curve was obtained in the initial standard test in one member of Group 1 and in 29 (19 per cent.) of Group 2.

Of the 37 members of Group 1 on whom the cortisone–glucose tolerance test was performed, the result was negative in 36, a diabetic curve being obtained from one subject, who had a normal curve in the standard test.

Of the 123 members of Group 2 who had given a normal curve in the standard test, the cortisone test was performed on 75, of whom eighteen (24 per cent.) gave a positive response in that the curve was clearly of the diabetic type.

In three of those classed as diabetic on the evidence of a borderline curve in the standard test the cortisone–glucose tolerance test produced a diabetic curve.

Similarly in six obese patients whose standard curve

was initially diabetic but had become normal after weight reduction the cortisone–glucose tolerance test produced again a classic diabetic curve.

The authors therefore conclude that in screening the apparently healthy relatives of diabetic patients three groups may emerge, the first (19 per cent.) giving an obvious diabetic curve with the standard glucose tolerance test, the second (24 per cent.) showing impaired carbohydrate tolerance only with the cortisone–glucose tolerance test, and the third giving no evidence of impaired carbohydrate tolerance in either test.

[This is an excellent study, and readers are advised to consult the original for details. The only point over which disagreement might arise is the old problem of what constitutes a normal glucose tolerance curve.]

J. N. Harris-Jones.

Biological Properties of the Adrenocorticotrophic Hormone. (Характеристика некоторых биологических свойств адренокортикотропного гормона.) ESKIN, I. A. (1955). *Problemy Endokr. Gormonoter*, **1**, 52. 4 figs, 9 refs.

The effect of the adrenocorticotrophic hormone (ACTH) secreted by the anterior lobe of the pituitary gland on the function of the adrenal cortex has long been known, but the elucidation of its influence on the pituitary itself and on other parts of the endocrine system is not yet complete. At the Institute of Experimental Endocrinology, Moscow, the author has studied the direct and indirect effects of ACTH on the sexual development and growth of the female rat, and concludes that although it delays the growth and development of the ovaries and uterus, it does not do so by hindering the production of gonadotrophic hormones by the pituitary, as it also slows up general growth.

It was observed that when ACTH is administered over a long period the reaction of the adrenal and thyroid glands diminishes, presumably owing to development of a resistance to the hormone. *H. W. Swann.*

Effects of Cortisone and Corticotrophin on the Human Adrenal Cortex. STONER, H. B., and WHITELEY, H. J. (1954). *Lancet*, **2**, 992. 14 refs.

The authors describe the anatomical and histochemical changes in the adrenal cortex of four adult patients who were receiving corticotrophin and of three who were receiving cortisone acetate at the time of death. The combined weight of the adrenal glands was determined after fixation in 10 per cent. formol–saline solution, and the width of the different zones of the cortex was measured in sections stained with haematoxylin and eosin. The physiological state of the cortex was assessed from the amount of sudanophilic and phenylhydrazine-reacting material present and also from the number and size of birefringent crystals seen after treatment of the glands with digitonin.

The combined weight of the adrenal glands of the patients who had received corticotrophin was above the upper limit of normal, while the width of the zona fasciculata was about twice the normal, this accounting for the total thickening of the cortex. The surfaces of the glands were often nodular owing to cortical overgrowth. The diminution in the amount of sudanophilic and phenylhydrazine-reacting material present and the reduction in the size and number of the birefringent crystals revealed an increased secretory activity. These changes were patchily distributed in both the zona glomerulosa and the zona fasciculata, indicating that the zonation of the adrenal cortex is of anatomical rather than physiological significance.

The effects of cortisone therapy were the reverse of these. The adrenal glands weighed less than half the normal; this was due to cortical atrophy, since the medulla was unchanged. There was atrophy of the zona fasciculata, but it was difficult to determine the width of each zone because of the distortion of the cortical architecture. The amount of sudanophilic, phenylhydrazine-reacting, and digitonin-birefringent material present was greatly increased, indicating secretory inactivity.

These findings show that cortical damage can be caused by therapeutic doses of cortisone; the authors therefore suggest that corticotrophin should be given instead of cortisone whenever possible, since these changes may be irreversible. *Richard de Alarcón.*

Clinical Studies on a New Long-Acting Preparation of Adrenocorticotrophic Pituitary Hormone containing Zinc. BONNER, C. D., and HOMBURGER, F. (1954). *Bull. New Engl. med. Cent.*, **16**, 159. 5 figs, 14 refs.

When corticotrophin (ACTH) is administered in a gelatin vehicle its action is prolonged. Recently it has been reported that the action of ACTH is not only further prolonged but is also enhanced if the hormone is precipitated with an insoluble zinc salt in aqueous suspension. The present authors, at the Tufts College Medical School, Boston, tried a carboxy-cellulose purified corticotrophin (Type A) with zinc hydroxide, the potency of which was 12·4 *U.S.P.* units per ml., in fifteen patients suffering from various chronic disorders and compared its effectiveness with that of a gelatin suspension of ACTH.

The potency of the zinc preparation and the duration of its effect were determined by the eosinophil response, the eosinophil count estimated before and 4 hours after intramuscular injection of forty units of various ACTH preparations being plotted on a graph. For control purposes results were recorded in all cases after administration of 2 ml. crude liver extract. When gelatin preparations of ACTH were used the eosinophil count generally returned to the pre-injection level within 48 hours; when, however, the zinc preparation was given the eosinophil count was depressed for 56 hours or longer. In two patients—one with pemphigus foliaceus and one with atopic dermatitis—whose minimum requirements of ACTH had been well established for many months, the zinc preparation proved to be considerably more potent than the gelatin suspension and its action more prolonged. In the authors' view this enhanced and prolonged action of the zinc preparation permits reduction in the dosage of ACTH and in the number of injections necessary; the preparation is also easier to handle than a gelatin suspension. *Nancy Gough.*

Comparative Study of Aldosterone and Other Adrenal Steroids in Adrenalectomized Dogs. SWINGLE, W. W., MAXWELL, R., BEN, M., BAKER, C., LEBRIE, S. J., and EISLER, M. (1954). *Endocrinology*, **55**, 813. 15 refs.

In a study of the comparative effects of aldosterone and three other adrenocortical steroids, carried out at the University of Princetown, New Jersey, four adrenalectomized dogs were tested with each steroid. These sixteen animals had been without adrenal glands for 1 to 4 years and had been maintained in good health on a single daily intramuscular injection of 0·5 mg. deoxycortone acetate in oil and a diet containing 1·47 g. sodium and 0·94 g. potassium. Each steroid in a 10 per cent. alcoholic solution was injected subcutaneously in two divided doses daily, the initial dose being gradually reduced to the minimum maintenance level and this dose continued for at least 10 days except in two of the animals treated with aldosterone. The minimum daily maintenance doses were approximately 10 μg. aldosterone, 125 to 250 μg. deoxycortone (DOC)—as compared with 300 to 500 μg. daily DOC in oil—and 5,000 μg. cortisone or hydrocortisone. A dose of only 0·3 mg. per kg. body weight per day of the 10 per cent. alcoholic solution of cortisone or hydrocortisone was necessary for maintenance, as compared with one of 1·86 mg. per kg. per day in the case of the micro-crystalline suspension of these steroids.

The onset of adrenal insufficiency was gradual when the dose was reduced below the minimum maintenance level. The first sign was a fall in arterial blood pressure, accompanied in two of the animals by normal serum levels of sodium and potassium, while a third showed a marked rise in serum potassium level.

The following conclusions were drawn:

(1) Aldosterone is 12 to 25 times more potent than deoxycortone.

(2) A larger dose of aldosterone is necessary to maintain the arterial blood pressure than to maintain a normal serum electrolyte pattern.

(3) Aldosterone is less efficient in preventing the accumulation of excess potassium in the serum than in retaining sodium; of three animals in which the potassium serum level exceeded 8·6 mEq. per litre when the sodium level was normal or only slightly reduced, two developed severe cardiac symptoms and prostration.

(4) The maintenance requirement of aldosterone is 500 times less than that of cortisone or hydrocortisone, but its carbohydrate-regulating activity is of course much weaker, although more powerful than that of deoxycortone. *Robert de Mowbray.*

Effect of Cortisone on Response to Endotoxin in Mature Rabbits. THOMAS, L., and SMITH, R. T. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 810. 11 refs.

The authors had previously observed in young rabbits that cortisone interfered with a protective mechanism, perhaps involving the reticuloendothelial system, against the vascular necrotizing action of injected endotoxin. In this further study carried out at the University of Minnesota Medical School, Minneapolis, 24 mature rabbits were given a daily injection of 10 mg. cortisone per kg. body weight on three successive days; on the third day meningococcal endotoxin was injected intravenously and the effect compared with that of the same dose of endotoxin administered to 24 untreated controls. Of the latter eighteen died within 18 hours, but in none of these was there evidence of renal cortical necrosis, nor was there in any of the survivors which were killed at 24 hours. Although only three of the 24 cortisone-treated animals died, it was found nevertheless that nine of this group showed renal cortical necrosis when killed and examined at 24 hours.

In a further study a group of six rabbits were given a single intramuscular injection of 10 mg. cortisone 6 hours before the injection of meningococcal endotoxin. They all survived for 24 hours, and when killed were found to be free from renal cortical necrosis. Of six controls given the endotoxin, but no cortisone, three died within 24 hours, but none developed renal lesions. In another similar experiment, it was found that cortisone prevented the early lethal reaction caused by small amounts of endotoxin following an injection of colloidal iron saccharate, but that it did not prevent the development of renal cortical necrosis. *B. Nordin.*

Life-Maintaining Action of 9-Alpha-Chloro Hydrocortisone Acetate in Adrenalectomized Rats. LEATHEM, J. H., and WOLF, R. C. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 724. 4 refs.

In a study carried out at Rutgers University, New Brunswick, on adrenalectomized immature male rats all the animals survived for at least 20 days when given 15 μg. daily chlorohydrocortisone acetate (CHCA), whereas ten times that amount of cortisone acetate was required to give the same protection. In similar animals 100 per cent. survival was also obtained with deoxycortone acetate in doses of 15 to 20 μg. A study of the gain in body weight showed that rats treated with cortisone acetate gained an average of only 13 g. in 20 days, whereas those maintained on CHCA gained an average of 56 g. To test the duration of action of the steroids, two groups of rats were given either a single injection of cortisone acetate (2·5 mg.) or CHCA (0·25 mg.) immediately after adrenalectomy; a third group of untreated animals acted as a control. The control animals survived for 7 days, the cortisone-treated rats 10·5 days, and the CHCA-treated animals 18·5 days. A group given CHCA together with a protein-free diet survived only 12·2 days. A single injection of deoxycortone acetate had no effect on survival. *B. Nordin.*

Arthritis following Use of Desoxycorticosterone Acetate and Cortisone. Occurrence in Patient with Adrenal Cortical Hypofunction. HURSH, L. M. (1955). *J. Amer. med. Ass.*, **157**, 1005. 1 fig., 7 refs.

Levels of 17-Hydroxycorticosteroids in Body Fluids. SANDBERG, A. A., EIK-NES, K., NELSON, D. H., and TYLER, F. H. (1954). *J. Lab. clin. Med.*, **43**, 874. 9 refs.